MASTER OF PHARMACY

IN

PHARMACEUTICS

Submitted by

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Under the guidance of

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DEPARTMENT OF PHARMACEUTICS

C.L.BAID MEHTA COLLEGE OF PHARMACY

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THORAIPAKKAM, CHENNAI-600097

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DESIGN AND EVALUATION OF FLUOXETINE ORODISPERSIBLE TABLETS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

Chennai

In partial fulfillment for the award of the degree of

MASTER OF PHARMACY

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First and foremost I would like to thank God. In the process of putting this book together I realized how true this gift of writing is for me. You given me the power to believe in my passion and pursue my dreams. I could never have done this without the faith I have in you, the Almighty.

It is a very exciting and memorable moment for me to express my immense gratitude and sincere thanks to my research guide and the chief architect of this work

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TABLE OF CONTENTS

ABBREVIATIONS

µm	Micrometer
µl	Micro liter

GMP	Good Manufacturing Practices
USP	United States Pharmacopeia
mg	Milligram
Gm	Gram
API	Active Pharmaceutical Ingredient
DT	Disintegration time
ND	Not detected
Rpm	Rotations per minute
MCC	Microcrystalline Cellulose
SLS	Sodium lauryl sulphate
CCS	Crosscarmellose sodium
SSG	Sodium starch glycolate
Min	Minute
ºC	Degree Celsius
C max	Maximum Concentration
T max	Maximum Time
Ppm	Parts per million

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DECLARATION

I hereby declare that the dissertation work entitled "**DESIGN AND EVALUATION OF FLUOXETINE ORODISPERSIBLE TABLETS**" Submitted in partial fulfillment for the award of the degree of Master of Pharmacy in Pharmaceutics to The TamilNadu Dr.MGR Medical University, Chennai, was carried out in PHARMATRAIN, Hyderabad, under the guidance and supervision of **Dr. U.UBAIDULLA.,** and institutional guide **Mr. G.N.V.CHANDRA SEKAR REDDY, M. Pharm.** I also declare that the matter embodied in it is a genuine work.

Introduction

Review of Literature

Aim and Objective

Plan of work

Drug profile

Excipients Profile

Materials and Methods

Results and Discussion

Bibliography

Conclusion

INTRODUCTION

Oral route of drug administration is most appealing route for delivery of drugs of various dosage forms. The tablets is one of the most preferred dosage form because of its ease of administration, accurate dosing and stability as compared to oral liquid dosage forms and when compared to capsules, tablets are more temper evident

1.1 TABLETS[1]

Tablets may be defined as solid unit pharmaceutical dosage forms containing drug substance with or without suitable Excipients and prepared by either compression or molding mehtods[1]. The first step in the development of dosage form is Preformulation, which can be defined as investigation of physicochemical properties of drug substance alone and when combined with Excipients. The main objective of Preformulation studies, is to develop stable and bioavilabel dosage form and study of factors affecting such stability, bioavailability and to optimize so as to formulate the best dosage form, here optimization of formulation means finding the best possible composition[2]. compressed tablets are formed by applying pressure, for which compression machines (tablet presses) are used and they are made from powdered crystalline or granular material, alone or in combination with binder, disintegrants, release polymers, lubricants and diluents and in some cases colorant.

1.1.1 Various Types of Tablets[2]

A. Oral tablets for ingestion

These tablets are meant to be swallowed intact along with a sufficient quantity of potable water. Exception is chewable tablet. Over 90% of the tablets manufactured today are ingested orally. This shows that this class of formulation is

the most popular worldwide and the major attention of the researcher is towards this direction.

1. Standard compressed tablets
2 Multiple compressed tablets
    a. Compression coated tablet
    b. Layered tablet
    c. Inlay tablet
3. Modified Release tablet
4. Delayed action tablet
5. Targeted tablet
    a. Floating tablet
    b. Colon targeting tablet
6. Chewable tablet
7. Dispersible tablet

B. Tablets used in the oral cavity

The tablets under this group are aimed release active pharmaceutical ingredient in oral cavity or to provide local action in this region. The tablets under this category avoids first-pass metabolism, decomposition in gastric environment, nauseatic sensations and gives rapid onset of action. The tablets formulated for this region are designed to fit in proper region of oral cavity.

1. Lozenges and troches
2. Sublingual tablet
3. Buccal tablet
4. Dental cones
5. Mouth dissolved tablet

C. Tablets administered by other routes

These tablets are administered by other route except for the oral cavity and so the drugs are avoided from passing through gastro intestinal tract. These tablets may be inserted into other body cavities or directly placed below the skin to be absorbed into systemic circulation from the site of application.

1. Vaginal tablet
2. Implants

D. Tablets used to prepare solution

The tablets under this category are required to be dissolved first in water or other solvents before administration or application. This solution may be for ingestion or parentral application or for topical use depending upon type of medicament used.

1. Effervescent tablet
2. Hypodermic tablet

1.2 FORMULATION OF TABLETS

In addition to active pharmaceutical agent (API), the tablets contain non drug substances called as Excipients, which include:

Table-1 Excipients in Tablet Formulation and Their Functions[2,3]

Diluents or Fillers	Diluents make the required bulk of the tablet when the drug dosage itself is inadequate to produce tablets of adequate weight and size.
Binders/ Granulating agents	Provides cohesiveness to powders, thus providing the necessary bonding to form granules.
Disintegrates	Facilitate a breakup or disintegration of the tablet when placed in an aqueous environment.
Antifrictional Agents	
Lubricants	Reduce the friction during tablet formation in a die and also during ejection from die cavity.
Anti adherents	Reduce sticking or adhesion of any of the tablet granulation or powder to the faces of the punches or to the die wall.
Glidants	Promote the flow of tablet granulation or powder mixture from hopper to the die cavity by reducing friction between the particles.
Miscellaneous	
Wetting agents	Aid water uptake during disintegration and assist drug dissolution.
Dissolution retardants	Retards the dissolution of active pharmaceutical ingredients.
Dissolution enhancers	Enhance the dissolution rate of active pharmaceutical ingredients.
Adsorbents	Retain large quantities of liquids without becoming wet; this property allows many oils, fluid extracts to be incorporated into tablets.
Buffers	Provide suitable micro environmental pH to get improved stability and / or bioavailability.
Antioxidants	Prevents oxidation and maintains the product stability.
Chelating agents	Protect against autoxidation; they act by forming complexes with the heavy metal ions which are often required to initiate oxidative reactions.
Preservatives	Prevent the growth of micro-organisms.
Colors & flavors	Provides attractiveness, increase patient compliance and product identification.
Sweeteners	Sweeteners are added to mask bitter taste of tablets

1.3 TABLET: MANUFACTURING METHODS[2, 3, 4]

1.3.1 Wet Granulation

The most widely used process of agglomeration in pharmaceutical industry is wet granulation. Wet granulation process simply involves wet massing of the powder blend with a granulating liquid, wet sizing, drying and compression.

Raw materials → Weighing → Screening → Wet mass → Sieving/Milling → Drying → Screening → Mixing → Compression

1.3.2 Dry Granulation

In dry granulation process the powder mixture is compressed without the use of heat and solvent. Two methods are used for dry granulation. The more widely used method is slugging, where the powder is pre compressed and the resulting tablet or slug are milled to yield the granules and the compressed to tablets.

Raw material → Weighing → Screen → Mixing → Slugging →Milling → Screening → Mixing → Compression

1.3.3 Direct Compression

Direct compression is a more efficient and economical process as compared to other processes, because it involves only dry blending and compaction of API and necessary excipients.

Raw material →Weighing → Screening → Mixing → Compression

1.3.4 Defects in Tablet Manufacturing [2, 3]

- **Lamination:** Separation of a tablet into two or more distinct horizontal layers.
- **Capping:** Partial or complete separation of top or bottom crowns of a tablet.
- **Chipping:** Breaking of tablet edges during compression or coating.

- **Cracking:** Fine cracks observed on the upper and lower central surface of tablets, or very rarely on the sidewall are referred to as 'Cracks'.
- **Picking:** In picking the tablet material adheres to the surface of the punches resulting in tablets with a pitted surface instead of a smooth surface.
- **Sticking:** The tablet material adheres to the die wall.
- **Mottling:** Unequal distribution of colour on the surface of coloured tablets.
- **Blotting:** Appearance of light or dark spots of colour on the tablet surface.
- **Double Impression:** It involves only those punches, which have a monogram or other engraving on them. Free travel or free rotation of either upper punch or lower punch during ejection of a tablet causes double impression.

1.4 ORAL DISINTEGRATING TABLETS

The most important drug delivery route is undoubtedly the oral route. It offers advantages of convenience of administration and potential manufacturing cost savings. Drugs that are administered orally, solid oral dosage forms in general and tablets in particular represent the preferred class of product. Today drug delivery companies are focusing on solid oral drug delivery systems that offer greater patient compliance and effective dosages. Tablet is the most popular among all dosage forms existing today because of its convenience of self administration, compactness and easy manufacturing. Many patients find it difficult to swallow tablets and hard gelatin capsules and do not take their medication as prescribed. In a survey conducted by Honda and Nakano, half of the patients experienced difficulty taking medication, such as tablet and capsule which results in a high incidence of non-compliance and ineffective therapy. The difficulty is experienced in particular by paediatric and geriatric patients, but it also applies to people who are ill in bed and

to those active working patients who are busy or traveling, especially those who have no access to water.[5] Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets offer an advantage for populations who have difficulty in swallowing. It has been reported that Dysphagia (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute[6].

1.4.1 Historical Perspective of ODT

Products of ODT technologies entered the market in the 1980's, have grown steadily in demand, and their product pipelines are rapidly expanding. The first ODT form of a drug to get approval from the US (FDA) was a Zydis ODT of Claritin (Loratadine) in December 1996. It was followed by a ZYDIS ODT formulation of Klonopin (Clonazepam) in December 1997, and a ZYDIS ODT formulation of Maxalt (Rizatriptan) in June 1998. CATALENT PHARMA SOLUTIONS in the U.K., CIMA LABS in the U.S. and TAKEDA Pharmaceutical Company in Japan lead in the development of ODTs[7].

Consumer Preferences for ODT's[8]

Recent market studies indicate that most of the patient population prefers ODTs to other dosage forms and would ask their doctors for ODTs (70%), purchase ODTs (70%), or prefer ODTs to regular tablets or liquids (>80%). In addition, several business needs are driving ODT technology development and the commercialization of new products such as the need for expanded product lines, improved life-cycle management, extended patent life, and marketing advantages[7,8].

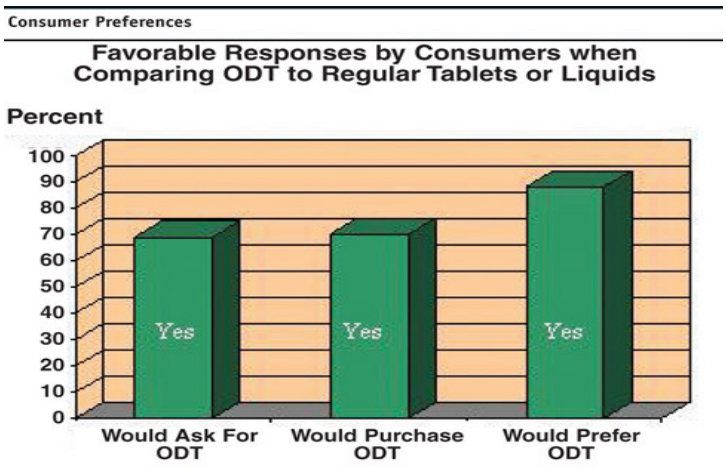


Figure-1 consumer's response on ODT's

1.4.2 Drug Selection Criteria

The ideal characteristics of a drug for orodispersible tablet include [9]

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odour drugs are unsuitable for ODT.

1.4.3 Important Criteria for Excipients used in the Formulation of ODT'S

- It must be able to disintegrate quickly.
- Their individual properties should not affect the ODTs.
- It should not have any interactions with drug and other excipients.
- It should not interfere in the efficacy and organoleptic properties of the product.
- When selecting binder a (single or combination of binders) care must be taken in the final integrity and stability of the product.
- The melting points of excipients used will be in the range of 30-350C.
- The binders may be in liquid, semi liquid, solid or polymeric mixtures[10].
- (Ex: Polyethylene glycol, cocoa butter, hydrogenated vegetable oils)

1.4.4 Advantages [11, 12]

- Easy to administer to the patient who cannot swallow such as pediatric, geriatric, bedridden, stroke victim and institutionalized patient (specially for mentally retarded and psychiatric patients)
- Pregastric absorption leading to increased bioavaibility rapid absorption of drugs from mouth, pharynx and oesophagus as saliva passes down to stomach, also avoids hepatic metabolism.
- Convenient for administration to travelling patients and busy people who do not have accesses to water.
- Excellent mouths feel property produced by use of flavours and sweetners help to change the perception of “medication as bitter pill” especially in pediatric population.
- Fast disintegration of tablets leads to quick dissolution and rapid absorption which may produce rapid onset of action.

- ODTs offer all the advantages of solid dosage forms and liquid dosage forms.
- Convenience of administration and accurate dosing compared to liquids.

1.4.5 Challenges in the Formulation of Orally Disintegrating Tablets

Palatability[13, 14]

As most drugs are unpalatable, orally disintegrating drug delivery systems usually contain the medicament in a taste-masked form. Delivery systems disintegrate or dissolve in patient's oral cavity, thus releasing the active ingredients which come in contact with the taste buds; hence, taste-masking of the drugs becomes critical to patient compliance

Mechanical strength[15, 16, 17]

In order to allow ODTs to disintegrate in the oral cavity, they are made of either very porous and soft-molded matrices or compressed into tablets with very low compression force, which makes the tablets friable and/or brittle, difficult to handle, and often requiring specialized peel-off blister packing that may add to the cost. Only few technologies can produce tablets that are sufficiently hard and durable to allow them to be packaged in multidose bottles, such as Wowtab® by Yamanouchi-Shaklee, and Durasolv® by CIMA labs.

Hygroscopicity[18]

Several orally disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, they need protection from humidity which calls for specialized product packaging

Amount of drug[13, 19]

The application of technologies used for ODTs is limited by the amount of drug that can be incorporated into each unit dose. For lyophilized dosage forms, the drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs. This parameter is particularly challenging when formulating a fast-dissolving oral films or wafers.

Aqueous solubility[20, 21]

Water-soluble drugs pose various formulation challenges because they form eutectic mixtures, which result in freezing-point depression and the formation of a glassy solid that may collapse upon drying because of loss of supporting structure during the sublimation process. Such collapse sometimes can be prevented by using various matrix-forming excipients such as Mannitol than can induce crystallinity and hence, impart rigidity to the amorphous composite.

Size of tablet[22]

The degree of ease when taking a tablet depends on its size. It has been reported that the easiest size of tablet to swallow is 7-8 mm while the easiest size to handle was one larger than 8 mm. Therefore, the tablet size that is both easy to take and easy to handle is difficult to achieve.

Table-2 Drugs Explored for Orally Disintegrating Tablets.[23]

Category	Drug
NSAIDS	Ketoprofen, Piroxicam, Paracetomol, Rofecoxib, Nimesulide, Ibuprofen
Anti ulcer	Famotidine, Lansoprazole
Anti parkinsonism	Selegiline
Anti depressants	Mitraxepine, Fluoxetine, Escitalopram Oxalate
Anti migrane	Sumatriptan, Rizatriptan benzoate, Zolmitriptan
Anti histaminics	Loratadine, Diphenhydramine, Meclizine
Hypnotics sedatives	Zolpidem, Clonazepam, Atenolol
Anti psychotics	Olanzepine, Pirenzepine, Risperidone
Anti emetics	Ramosetoron HCl, Ondansetron
Miscellaneous	Ethenzamide, Baclofen, Hydrochlorthiazide, Tramodol Hcl, Propyphenazone, Spiranolactone, Phloroglucinol, Sildenafil

1.5 VARIOUS APPROACHES EMPLOYED IN MANUFACTURE OF ODT'S

There are number of techniques generally employed in the formulation of orally disintegrating dosage forms. These techniques have their own advantages as well as disadvantages and are described below:

1.5.1 Direct Compression

Direct compression is one of the popular techniques for preparation of these dosage forms. The advantages of this method include easy implementation, use of conventional equipments along with commonly available excipients, limited number of processing steps and cost effectiveness. Disintegration and solubilization of directly compressed tablets depend on single or combined action of disintegrants, water-soluble excipients and effervescent agents. The basic principle involved in development of these dosage forms using this technique is addition of Superdisintegrants in optimum concentrations so as to achieve rapid disintegration along with pleasant mouth feel [24]. It is considered as the best method to prepare orally disintegrating dosage forms since the prepared tablets offer higher disintegration due to absence of binder and low moisture contents [25]. This approach is also considered as disintegrant addition technology.

1.5.2 Freeze Drying

Freeze drying or lyophilization is a process in which solvent is removed from a frozen drug solution or suspension containing structure forming excipients. Tablets formulated by this technique are usually very light and porous in nature which allows their rapid dissolution. Glassy amorphous porous structure of excipients as well as the drug substance produced with freeze drying results in enhanced dissolution. Freeze drying process normally consists of three steps:

- Material is frozen to bring it below the eutectic point.
- Primary drying to reduce the moisture around 4% w/w of dry product.

- Secondary drying to reduce the bound moisture upto required final volume.

Entire freeze drying process is carried out at non elevated temperature; therefore, nullifying adverse thermal effects that may affect drug stability during processing[24]. R.P. Scherer patented *zydis technology* utilizing lyophilization or freeze drying process in development of mouth dissolving tablets on the basis of patents issued to Gregory *et al* [26,27]. Corveleyn Sam *et al* also prepared rapidly disintegrating tablets by lyophilization [28].

1.5.3 Sublimation

Because of low porosity, compressed tablets containing highly water-soluble excipients as tablet matrix material often do not dissolve rapidly in water. Some inert volatile substances like urea, urethane, ammonium carbonate, naphthalene, camphor etc. are added to other tablet excipients and blend is compressed into tablet. Removal of volatile substances by sublimation generates a porous structure. Various steps involved in sublimation process are shown in Figure 1. Additionally several solvents like cyclohexane and benzene etc. can also be used as pore forming agents.

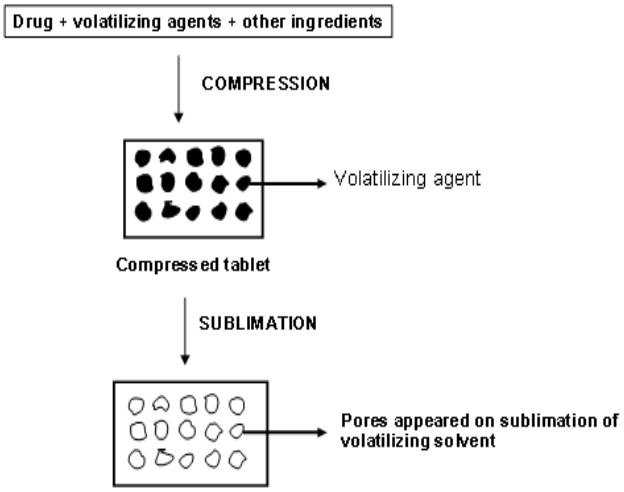


Figure 2: Steps involved in sublimation process

Koizumi *et al* formulated rapidly saliva soluble tablets using camphor as subliming agent. The tablets were subjected to vacuum at 80ºC for 30 min. to

eliminate camphor and thus create pores in the tablet. Porous tablet exhibits good mechanical strength and dissolve quickly[29]. Gohel M. *et al* prepared mouth dissolving tablets of nimesulide using vacuum drying technique and found that it would be an effective alternative approach compared to the use of more expensive adjuvants in the formulation of these dosage forms [30]

1.5.4 Moulding

Moulded tablets are designed to facilitate the absorption of active ingredients through mucosal linings of mouth. This is achieved by complete and rapid dissolution of the tablet using water soluble ingredients. Moulded tablets disintegrate more rapidly and offer improved taste because of the dispersion matrix which is generally prepared from water soluble sugars. Powdered blend (containing drug and excipients like binding agents - sucrose, acacia, PVP etc.) is pushed through a very fine screen (to ensure rapid dissolution) and then moistened with a hydroalcoholic solvent and moulded into tablets under pressure lower than employed for conventional compressed tablets. The solvent is later removed by air drying. A porous structure that enhances dissolution prepared by using water soluble ingredients meant to be absorbed through mucosal lining of mouth, thus increasing bioavailability and decreasing first pass metabolism of certain drugs.

1.5.5 Spray Drying

This technique is based upon the use of a particulate support matrix prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. Allen *et al* utilized this process for preparing ODTs. These formulations consisted of hydrolyzed/unhydrolyzed gelatin as supporting agent for matrix, mannitol as bulking agent, and sodium starch glycolate or croscarmellose sodium as disintegrating agent. Disintegration and dissolution were further improved by adding effervescent components, i.e. citric acid and sodium bicarbonate. The formulation was finally spray dried to yield a porous powder [31].

1.5.6 Mass Extrusion

This technology consist of softening the active blend using a solvent mixture of water soluble Polyethylene glycol with methanol and expulsion of softened mass through the extruder or syringe to obtain cylinder of the product into even segments employing heated blade to form tablet. The dried cylinder can also be utilized for coating the granules of bitter drugs and there by masking their taste[31,32]

1.5.7 Cotton Candy Process

This process is so named as it utilizes an inimitable spinning mechanism to produce floss like crystalline structure, which mimics cotton candy. This technique involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to have better flow properties and compressibility. This matrix is milled and blended with active ingredients as well as excipients and subsequently compressed to ODTs. This process can accommodate high doses of drug and offers improved mechanical strength. However, high process temperature limits the use of this process[31.]

1.5.8 Phase Transition

Kuno *etal* proposed a novel method to prepare ODTs with sufficient hardness by involving the phase transition of sugar alcohol. In this technique, ODTs are produced by compressing and subsequently heating tablets that contain two sugar alcohols, one with high and other with a low melting point. Heating process enhances the bonding among particles leading to sufficient Hardness of tablets which was otherwise lacking owing to low/little compatibility [33].

1.5.9 Melt Granulation

Melt granulation is a process in which pharmaceutical powders are efficiently agglomerated by the use of binder which can be a molten liquid, a solid or a solid that melts during the process. For accomplishing this process, high shear mixers are utilized, where the product temperature is raised above the melting point of binder by a heating jacket or by the heat of friction generated by impeller blades. Perissutti *et al* prepared carbamazepine fast-release tablets by melt granulation technique using polyethylene glycol 4000 as a melting binder and lactose monohydrate as hydrophilic filler [34, 35.]

1.6 IMPORTANT PATENTED TECHNOLOGIES FOR FAST DISSOLVING TABLETS[36-40]

Zydis Technology

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process.

Durasolv Technology

Durasolv is the patented technology of CIMA labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabulating equipment and have good rigidity. These can be packaged

into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

Orasolv Technology

CIMA labs have developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable.

Flash Dose Technology

Flash dose technology has been patented by fuisz. Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as “floss”. Shear form matrices are prepared by flash heat processing.

Wow tab Technology

Wow tab technology is patented by Yamanouchi Pharmaceutical Co.WOW means “Without Water”. In this process, combination of low mould ability saccharides and high mould ability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mould ability saccharide (eg. lactose, glucose, and mannitol) and granulated with a high mould ability saccharide (eg. Maltose, oligosaccharides) and compressed into tablet.

Flash tab Technology

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques

like coacervation, micro encapsulation and extrusion spheronisation. All the processing utilized conventional tabletting technology.

OraQuick

The OraQuick fast-dissolving/disintegrating tablet formulation utilizes a patent taste masking technology. KV Pharmaceutical claims its microsphere technology, known as MicroMask, has superior mouthfeel over taste-masking alternatives. The taste masking process does not utilize solvents of any kind, and therefore leads to faster and more efficient production.

Quick –Dis Technology

Lavipharm Laboratories Inc. (Lavipharm) has invented an ideal intraoral fast-dissolving drug delivery system, which satisfies the unmet needs of the market. The novel intraoral drug delivery system, trademarked Quick- Dis™, is Lavipharm's proprietary patented technology and is a thin, flexible, and quick-dissolving film. The film is placed on the top or the floor of the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption. The Quick-Dis™ drug delivery system can be provided in various packaging configurations, ranging from unit dose pouches to multiple-dose blister packages. The typical disintegration time, which is defined as the time at which the film begins to break when brought into contact with water, is only 5 to 10 seconds for the Quick- Dis™ film with a thickness of 2 mm. drug delivery system is 50% released within 30 seconds and 95% within 1 minute.

Durasolv Technology

DuraSolv is Cima's second-generation fast-dissolving/disintegrating tablet formulation. Produced in a fashion similar to OraSolv, DuraSolv has much higher mechanical strength than its predecessor due to the use of higher compaction pressures during tabulating. DuraSolv tablets are prepared by using conventional tabletting equipment and have good rigidity (friability less than that 2%). The DuraSolv product is thus produced in a faster and more cost-effective manner.

DuraSolv is so durable that it can be packaged in traditional blister packaging, pouches or vials. One disadvantage of DuraSolv is that the technology is not compatible with larger doses of active ingredients, because the formulation is subjected to such high pressures on compaction. Unlike OraSolv, the structural integrity of any taste masking may be compromised with high drug doses. The drug powder coating in DuraSolv may become fractured during compaction, exposing the bitter-tasting drug to a patient's taste buds. Therefore, the DuraSolv technology is best suited for formulations including relatively small doses of active compound.

Sheaform Technology

This technology make Sheaform matrix consisting of floss preparation. Floss is produced by subjecting to a feedshock containing a sugar to flash heat processing.

Ceform Technology

In this technology microspheres containing active ingredient are prepared. Basic requirement of this technology is placing dry powder containing either pure drug or special blend of drug and excipients. The microspheres then mixed and compressed into previously selected oral dosage form.

Lyoc (Laboratories L. Lafon, Maisons Alfort , France)

Lyoc utilizes a freeze drying process but differ from Zydis in that the product is frozen on the freeze dryer shelves. To prevent sedimentation during this process, these formulations require a large proportion of undissolved inert filler (mannitol), to increase the viscosity of the inprocess suspension. The high proportion of filler reduces the potential porosity of the dried dosage form and results in denser tablets with disintegration rates that are Comparable with the loosely compressed fast melt formulations.

Pharmaburst technology

Pharmaburst™ is a "Quick Dissolve" delivery system patented by SPI Pharma. Pharmaburst is a co-processed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punch facesmouldablilty saccharides are used to obtain rapid melting strong tablet. The active ingredient mixes with low mouldablilty saccharides.

Frosta technology

Akina patents this technology. It utilizes the concept of formulating plastic granules and compressing them at low pressure to produce strong tablets with high porosity. Plastic granules composed of porous and plastic material, water penetration enhancer, and binder. The process involves mixing the porous plastic material with water penetration enhancer followed by granulating with binder. The tablets obtained have excellent hardness and rapid disintegration time ranging from 15 to 30 sec depending on size of tablet.

Nano technology

For fast dissolving tablets, Elan's proprietary NanoCrystal technology can enable formulation and improve compound activity and final product characteristics. Decreasing particle size increases the surface area, which leads to an increase in dissolution rate. This can be accomplished predictably and efficiently using NanoCrystal technology. NanoCrystal™ Fast dissolving technology provides for:

- Pharmacokinetic benefits of orally administered nanoparticles (<2 microns) in the form of a rapidly disintegrating tablet matrix
- Product differentiation based upon a combination of proprietary and patent-protected technology elements.
- Cost-effective manufacturing processes that utilize conventional, scalable unit operations.

Table-3 ODT Patented Technologies and Corresponding Commercial Products [41]

Technologies	Company name	Products on market
DuraSolv®, OraSolv®	CIMA	Tempra®, FirsTabs, Trimainic ®, Softchews, Remeron®, SolTabs, Zomig® Rapimelt, Nulev®, Alavert®, Parcopa, Niravam, Clarinex Redi Tabs
Flash Dose	Biovail	Neruofen
Flashtab	Ethypharm	Nurofen
Kryotab	Biotron	None
OraQuick	KV Pharmaceutical	None
Quick-Dis	Lavipharm	Lab Film none
Rapitrol™	Shire Lab	None
Slow-Dis™	Lavipharm Lab	Film none
WOWTAB	Yamanouchi	Benadryl Fastmelt
Advatab	Eurand	None
Zydis	Cardinal Health	Maxalt MLT, Claritin Reditabs, Zyprexa Zydis, Zofran ODT
Lyoc	Cephalon	Proxalyoc (piroxicam), Paralyoc (paracetamol), SpasponLyoc (loperamide)

1.7 POSSIBLE BENEFITS OF ORALLY DISINTEGRATING DRUGS[42,43.]

Clinical

- ✓ Improved drug absorption
- ✓ Faster onset of action
- ✓ Minimized first-pass effect
- ✓ Improved bioavailability

Medical

- ✓ No tablet or capsule to swallow or chew.
- ✓ Better taste, no water needed.
- ✓ Improved safety and efficacy.
- ✓ Improved compliance
- ✓ The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

Technical

- ✓ More accurate dosing than liquid products.
- ✓ Can use sugars and other excipients that are generally recognized as safe.
- ✓ Improved stability because of unit-dose packaging.
- ✓ Manufacturing with common process and conventional equipment.

Business

- ✓ Unique product differentiation
- ✓ Value-added product line extension
- ✓ Marketing exclusivity
- ✓ Extended patent protection
- ✓ Product differentiation
- ✓ Line extension and life cycle management.
- ✓ Exclusivity of product promotion

1.8 TASTE

Taste is a sensation, which is realized when a substance such as food, beverages or drug is placed in the oral cavity. This sensation is the result of signal transduction from the receptor organ for taste, commonly known as taste buds. These taste buds contain very sensitive nerve endings, which produce and transmit electrical impulses via the seventh, ninth and tenth cranial nerves to those areas of the brain, which are devoted to the perception of the taste buds.[44]

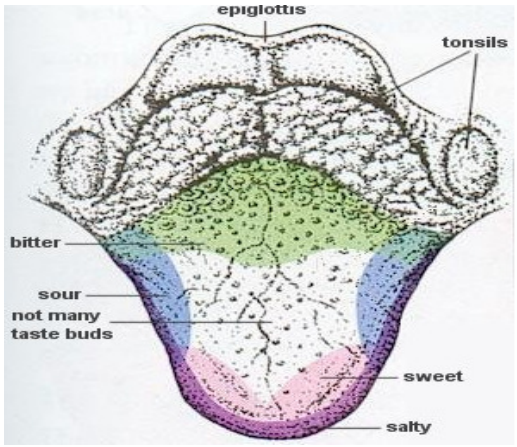


Figure 3: Tongue with localized taste buds.[45]

1.8.1 Anatomy and Physiology of Tongue

Physiologically, taste is a sensory response resulting from a chemical stimulation of taste buds on the tongue. The sense of taste is conducted to the brain by a process called taste transduction. This process begins with the interaction of tastant (i.e., food or medicine) with taste receptor cells in the taste buds. The tastant binds with G-protein coupled receptors in the cells, triggering the release of a G-protein called gustducin. Taste sensation begins when gustducin activates the effector enzymes phosphodiesterase 1A or phospholipase C β-2. The effector enzymes then change the intracellular levels of second messengers such as cyclic adenosine monophosphate (cAMP), inositol 1, 4, 5 triphosphate (IP3), and idacylglycerol (DAG). The second messengers activate ion channels, including calcium channels inside the cell, and sodium, potassium and calcium channels on the

extracellular membrane. This ionization depolarizes the cell, causing the release of neurotransmitters that send a nerve impulse to the brain that carries the signal of taste.[46]

In mammal's taste buds are aggregations of 30-100 individual elongated "intraepithelial" cells, which are often embedded in specialization of surrounding epithelium, termed papillae. At the apex of taste bud, microvillus process protrudes through a small opening, the taste pore, into the oral milieu. At the base of the taste bud, afferent taste bud, afferent taste nerve invade the bud and ramify extensively, each fibre typically synapse with multiple receptor cells within the taste bud.

The taste buds are found on three types of papillae on the tongue.

1. A large number of taste buds are on the wall of the troughs that surround the circumvallated papillae, which forms 'V' line on the posterior surface of the tongue.
2. Moderate numbers of taste buds are on fungi from papillae over the flat anterior surface of the tongue.
3. Moderate numbers are on the foliate papillae located in the folds along the lateral surface of the tongue.
4. Additional taste buds are located on the palate and few on the tonsillar pillars, the epiglottis and even in the proximal esophagus.

1.8.2 Innervations of Tongue

The receptor cell does not have axons. Transmitter relays information onto terminals of sensory fibers. These fibers arise from the ganglion cells of the cranial nerves VII (Facial – branch called the chorda tympani) and IX.

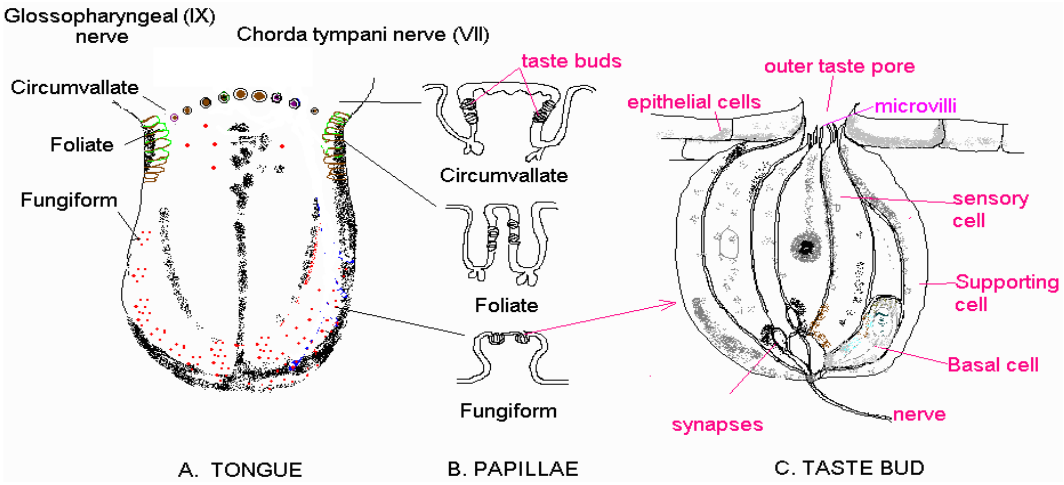


Figure 4: Papillae and taste buds[47]

1.8.3 Type of Taste

There are five basic tastes i.e., sour, salty, sweet, bitter, and "umami". These are called the *primary sensations of taste.*

a) **Sour Taste:** Acids cause the sour taste, that is, by the hydrogen ion concentration, and the intensity of this taste sensation is approximately proportional to the *logarithm of the hydrogen ion concentration.* That is, the more acidic the food, the stronger the sour sensation becomes.

b) **Salty Taste:** Ionized salts elicit the salty taste, mainly by the sodium ion concentration. The quality of the taste varies somewhat from one salt to another, because some salts elicit other taste sensations in addition to saltiness. The cations of the salts, especially sodium cations, are mainly responsible for the salty taste, but the anions also contribute to a lesser extent.

c) **Sweet Taste:** The sweet taste is not caused by any single class of chemicals. Some of the types of chemicals that cause this taste include sugars, glycols, alcohols, aldehydes, ketones, amides, esters, some acids, some small proteins, sulfonic acids, halogenated acids,

and inorganic salts of lead and beryllium. Most of the substances that cause a sweet taste are specifically organic chemicals. Slight changes in the chemical structure, such as addition of a simple radical, can often change the substance from sweet to bitter.

d) **Bitter Taste:** The bitter taste, like the sweet taste, is not caused by any single type of chemical agent. Here again, the substances that give the bitter taste are almost entirely organic substances. Two particular classes of substances are especially likely to cause bitter taste sensations: (i) long-chain organic substances that contain nitrogen, and (ii) alkaloids. The alkaloids include many of the drugs used in medicines, such as quinine, caffeine, strychnine, and nicotine. Some substances that at first taste sweet have a bitter aftertaste. This is true with saccharin, which makes this substance objectionable to some people. The bitter taste, when it occurs in high intensity, usually causes the person or animal to reject the food. This is an important function of the bitter taste sensation, because many deadly toxins found in poisonous plants are alkaloids, and virtually all of these cause intensely bitter taste, usually followed by rejection of the food.

e) **Umami Taste:** *Umami* is a Japanese word (meaning "delicious") designating a pleasant taste sensation that is qualitatively different from sour, salty, sweet, or bitter. Umami is the dominant taste of food containing L-glutamate, such as meat extracts and aging cheese, and some physiologists consider it to be a separate, fifth category of primary taste stimuli. A taste receptor for L-glutamate may be related to one of the glutamate receptors expressed in neuronal synapses of the brain. However, the precise molecular mechanisms responsible for umami taste are still unclear.

1.8.4 Mechanism of Stimulation of Taste

The membrane of the taste cell, like that of most other sensory receptor cells, is negatively charged on the inside with respect to the outside. Application of a taste substance to the taste hairs causes partial loss of this negative potential-that is, the taste cell becomes *depolarized.* In most instances, the decrease in potential, within a wide range, is approximately proportional to the logarithm of concentration of the stimulating substance. This *change in electrical potential* in the taste cell is called the *receptor potential* for taste.

The mechanism by which most stimulating substances react with the taste villi to initiate the receptor potential is by binding of the taste chemical to a protein receptor molecule that lies on the outer surface of the taste receptor cell near to or protruding through a villus membrane. This, in turn, opens ion channels, which allows positively charged sodium ions or hydrogen ions to enter and depolarize the normal negativity of the cell. Then the taste chemical itself is gradually washed away from the taste villus by the saliva, which removes the stimulus.

The type of receptor protein in each taste villus determines the type of taste that will be perceived. For sodium ions and hydrogen ions, which elicit salty and sour taste sensations, respectively, the receptor proteins open specific ion channels in the apical membranes of the taste cells, thereby activating the receptors. However, for the sweet and bitter taste sensations, the portions of the receptor protein molecules that protrude through the apical membranes activate *second-messenger transmitter substances* inside the taste cells, and these second messengers cause intracellular chemical changes that elicit the taste signals.

On first application of the taste stimulus, the rate of discharge of the nerve fibers from taste buds rises to a peak in a small fraction of a second but then adapts within the next few seconds back to a lower, steady level as long as the taste stimulus remains. Thus, the taste nerve transmits a strong immediate signal, and a weaker continuous signal is transmitted as long as the taste bud is exposed to the taste stimulus.[48]

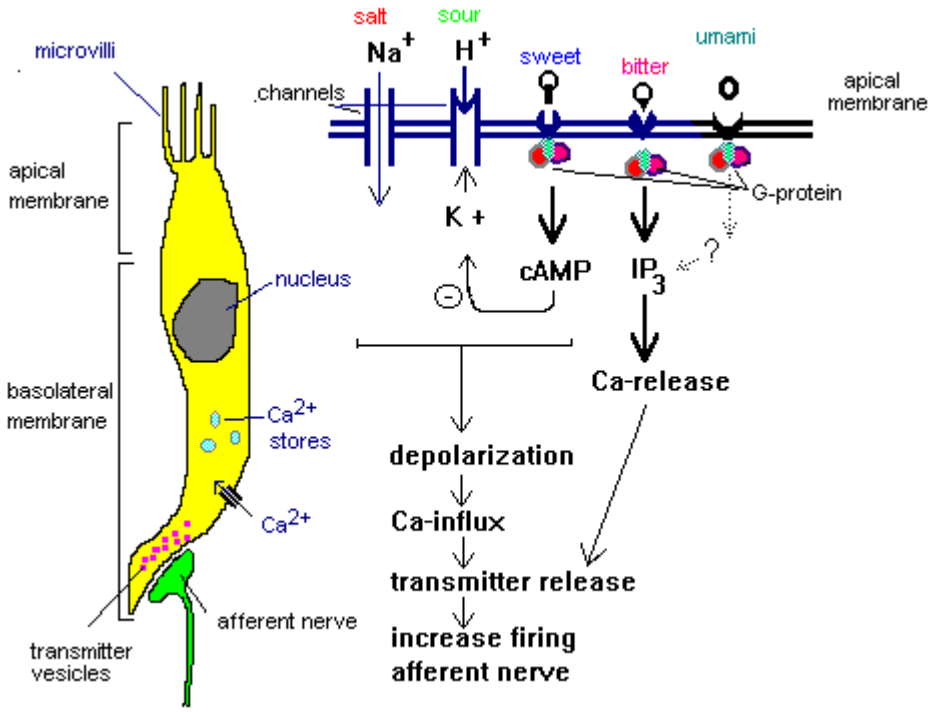


Figure 5: A taste receptor cell[49]

1.9 TASTE MASKING OF ORAL PHARMACEUTICALS

Taste masking is of critical importance for active ingredients with an unpleasant bitter taste, due to the need for increased patient compliance. Taste masking technology involves the development of a system that prevents the active substance interacting with the taste buds, thereby eliminating or reducing the negative sensory response. There are three general taste masking principles, the use of a physical barrier, chemical or solubility modification, and solid dispersions, each of them further subdivided into several methods. Additionally, unique platforms such as orally disintegrating and chewable tablets, applicable for taste masking have been extensively employed.[50]

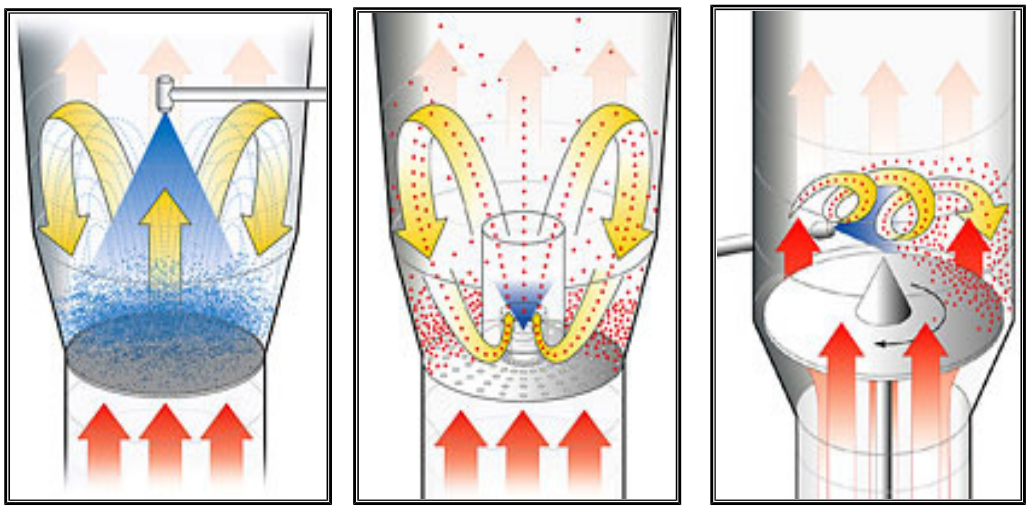
Taste masking of drug may be achieved with preventing the exposure of drug to the tongue through processing or adding competing taste-masking agents. Exposure of solubilized drug to the oral cavity can be prevented by encapsulation in polymer systems or complexation. The approaches are as follows:

A) Layer/Coat Process

The layering process involves deposition of successive layers of an active compound onto the granules of the inert starter seeds such as sugar spheres or microcrystalline cellulose beads. Sugar spheres (Non Pareil) or microcrystalline spheres (Celpheres) can be used as initial substrate in the preparation of beads by the layering process. In the layering process, the bitter drug is dissolved or dispersed in an aqueous or non-aqueous solvent, depending on its solubility characteristics and ease of processing. Binder is added to the solution to form liquid bridges between the primary particles. Most commonly used binders are gelatin, povidone, carboxymethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), and maltodextrin.[51] In solution form, the drug is completely soluble in the solvent, while in dispersed form, the drug is either micronized before adding into the solvent or the solvent containing dispersed drug is subjected to wet milling using a high-shear mixer to micronize in solution. It is desirable that the ratio of particle size of the drug to the size of the beads is about 1:10. In the layering process, drug layering up to 100–150% in weight is achievable, beyond which drug layering may cause excessive grittiness because of increased particle size of the granules when incorporated into a dosage form. A potential disadvantage encountered during drug layering process is the possibility of drug recrystallizing into different polymorphs upon completion of the process.

After the drug is layered over an inert starting material, it is then coated with a polymer that retards dissolution in the oral cavity. Two mechanisms to prevent dissolution are predominantly used, either a polymer that slows down dissolution across all pHs or a polymer that does not dissolve in the pH of the saliva but dissolves rapidly in the gastric fluid of the stomach. The various polymers used for taste-masking purpose are Eudragit E 100, ethylcellulose, HPMC, HPC polyvinyl alcohol, and polyvinyl acetate. The polymer is dissolved in an aqueous or non-aqueous solvent depending on its solubility characteristic and antitack agents such as talc, magnesium stearate, and cab-o-sil are added to improve processing and prevent agglomeration. Sometimes taste masking is possible by combining layer/coat in a single process, i.e., incorporating the drug in solution/suspension

form containing a polymer that serves both as a binder and as a taste-masking agent and then depositing the drug onto beads.



(a) *(b)* *(c)*

Figure 6: **Types of coating. (a) Top spray batch fluid coating. (b) Bottom spray batch fluid coating. (c) Tangential spray batch fluid coating.**[52]

B) Granulation

Taste masking by granulation is achieved by decreasing the surface area of the drug by increasing its particle size. The additional benefit obtained is ease of processing for tablet compression as the majority of drugs have a low bulk density. Additionally, polymers that serve as binders and taste-masking agents may be incorporated, which reduce the perception of taste. Granulation may be achieved with or without the use of a solvent. Dry granulation involves the use of forming compacts/slugs that are milled for blending. Wet granulation can be achieved by using the fluid bed process or high-shear granulation. In the fluid bed process, the drug is suspended in the bed with air, and a binder is sprayed from the top. The granules formed are porous and not amenable to further processing like coating. In high-shear granulation, the granule formation occurs by spraying a liquid binder onto drug/mixture of drugs with excipients that are being agitated by combined action of an impeller and chopper. The granules obtained are dense and may be used

directly or coated further in a fluid bed. This approach is suitable for high-dose drugs (>50 mg) with unpleasant taste.

C) Spray Drying

For taste-masking application, the drug is either dissolved or dispersed along with bulking agent (polymer) and, occasionally, a binding agent is also added if required, in a suitable solvent. Spray drying consists of four stages: atomization of feed into a spray, spray–air contact (mixing and flow), drying of spray (moisture/volatiles evaporation), and separation of dried product from the air.[53] The solvent used for spray drying process may be aqueous or non-aqueous. Product obtained upon spray drying yields high porosity granules or beads containing encapsulated drug. Some unintended effects include formation of solid dispersions of the drug owing to recrystallization and thermal degradation for temperature-sensitive drugs.

D) Complexation

Taste masking by inclusion complexation is possible by physically entrapping the drug in cone-shaped structures called cyclodextrins.[54] Cyclodextrins are bucket shaped oligosaccharides produced from starch. Owing to their peculiar structure and shape, they possess the ability to entrap guest molecules in their internal cavity. Drug inclusion complexes can be formed by a variety of techniques that depend on the property of the drug, the equilibrium kinetics, other formulation ingredients, processes, and the final dosage form desired. In all these processes, a small amount of water is required to achieve thermodynamic equilibrium. The initial equilibrium to form the complex is very rapid; the final equilibrium takes a longer time. The drug, once inside the cyclodextrin cavity, makes conformational changes to itself so as to attach itself to the complex and to take maximum advantage of the weak vander waals forces. Complexation is also possible through the use of ion-exchange resins. Both anionic and cationic types are available.[55] The preparation of the taste-masked complex involves suspending the resin in a solvent in which the drug is dissolved. For liquid preparations, the drug–resin complex can be used as is.

For solid dosage forms, the complex may be processed by filtration or direct drying. Drug loading up to 50% is possible with this process. Some commercially available ion-exchange resins that may be used for taste masking are based on methacrylic acid and divinyl benzene and styrene divinyl benzene polymer.[56]

E) Psychological Modulation of Bitterness

Taste masking with addition of competing agents involves modulating the psychological perception of bitterness. To understand this better, the theory of perception of taste is in order. The biochemical and physiological basis of bitterness has been summarized recently[6, 57]. There are two theories. One theory contends that receptors for common taste stimuli such as salt, bitter, and sweet are present in specific locations of the tongue. The second theory contends that taste buds respond to all stimuli to a different extent. Regardless of the mechanism, taste masking is achieved by the addition of specific inhibitors to suppress the stimuli. This approach is likely to involve the use of an inhibitor specific to the taste masking of the drug in question. In general, there is no specific universal inhibitor available, which will mask all the taste stimuli.

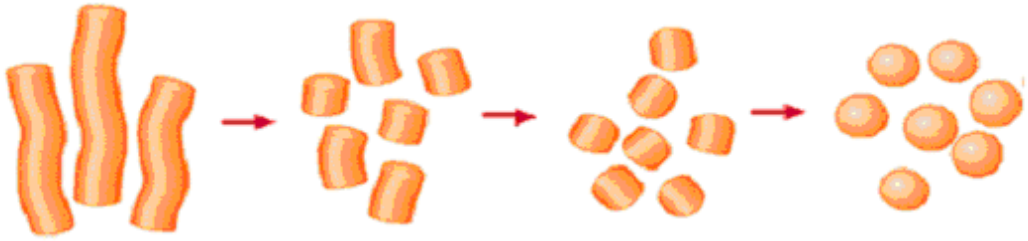
F) Coacervation

Coacervation leads to formation of a microencapsulated form of drug. The process primarily consists of formation of three immiscible phases, formation of the coat, and deposition of the coat. The formation of the three immiscible phases is accomplished by dispersing the core particles in a polymer solution. A phase separation is then induced by changing the temperature of the polymer solution, addition of a salt and nonsolvent, or by inducing a polymer–polymer interaction. This leads to deposition of the polymer coat on the core material under constant stirring. The core particles coated by the polymer are then separated from the liquid phase by thermal, cross-linking, or desolvation techniques leading to rigidization of the coat.

G) Extrusion Spheronization

The process begins with the blending of dry powders followed by granulation. The granulation is different from conventional granulation as the end point is determined by the consistency of the paste suitable for passing through an extruder. After passing through the extruder, the granulate is in the form of rods. The rods can then be passed through a spheronizer to form pellets, which are then dried. An advantage touted for extrusion spheronization is the formation of more spherical pellets compared to wet granulation.[57] Hot-melt extrusion involves passing a molten solid dispersion of the drug through a extruder to obtain pellets. The hot-melt extrudate consists of drug dispersed in a molten hydrophilic matrix, which is then passed through an orifice in the extruder. The extruder paste can then be passed through a spheronizer to obtain pellets that are subsequently cooled. This process is primarily used for increasing the solubility of poorly soluble drugs as it leads to formation of amorphous form of the drug; however, the appropriate choice of polymers could lend itself to taste masking. The advantage touted for this is better control of particle size of the pellets and absence of the use of solvents.

Figure 7: Extruder and spheronizer[58]



Extruded product Breaking up Spheronizing

Figure 8: Process of pellet formation[58]

1.10 SUPERDISINTEGRANTS AND ODT[59]

Superdisintegrant plays the major role in oral disintegrating tablet. The disintegration efficiency is based on the force-equivalent concept (the combined measurement of swelling force development and amount of water absorption). Superdisintegrants are generally used at a low level in the solid dosage form, typically 1 – 10 % by weight relative to the total weight of the dosage unit.

Common disintegrants used are Croscarmellose sodium (Vivasol, Ac-Di-Sol), Crospovidone (Polyplasdone), Carmellose (NS-300), Carmellose calcium (ECG-505), Sodium starch glycolate (SSG) etc. Recently few ion exchange resins (e.g. Indion 414) are found to have superdisintegrant property and are widely used in pharmaceutical industry.

1.10.1 Method of Addition of Disintegrants

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are three methods of incorporating disintegrating agents into the tablet:

I. Internal Addition (Intragranular)

II. External Addition (Extragranular)

III. Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles.

1.10.2 Mechanism of Tablet Disintegrants[59]

The tablets were broken into small pieces and then produces a homogeneous suspension which is based on the following mechanisms:

Capillary action/ Water wicking

Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. The ability of a disintegrant to draw water into the porous network of a tablet is essential for effective disintegration. Wicking is not necessarily accompanied by a volume increase.

By Swelling

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate into the tablet and disintegration again slows down.

Air expansion /Heat of wetting

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet.

Due to disintegrating particle/particle repulsive forces

Another mechanism of disintegration attempts to explain the swelling of tablet made with 'non-swellable' disintegrants. Non-swelling particles cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

Due to deformation

During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. This increase in size of the deformed particles produces a breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

Due to release of gases

Carbon dioxide is released within tablets on wetting due to interaction between bicarbonate and carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

By Enzymatic reaction

Here, enzymes presents in the body act as disintegrants. These enzymes destroy the binding action of binder and helps in disintegration.

Mechanism of Action of Superdisintegrant

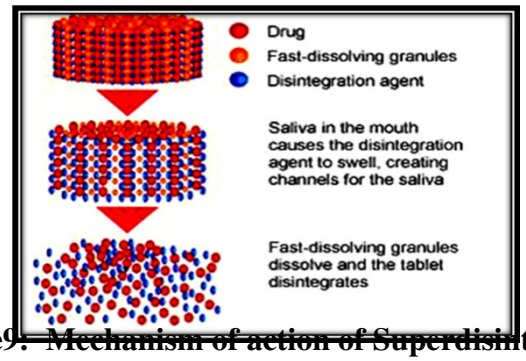


Figure9. Mechanism of action of Superdisintegrant

Table-4 Superdisintegrants Employed in ODTs.[60,61.]

Superdisintegrant	Nature	Properties	Mechanism
Crosspovidone	Crosslinked homo polymer of N-vinyl-2-pyrrolidone	Particle size - 100ìm. Insoluble in water. Gives smoother mouth feel.	Both swelling and wicking
Cross carmellose sodium	Cross-linked form of sodium CMC	Particle size - 200ìm. Insoluble in water.	Swelling
Sodium starch glycolate	Crosslinked low substituted carboxy methyl ether of poly-glucopyranose	Particle size - 140mesh. Insoluble in organic solvents, disperses in cold water and settles in the form of a highly saturated layer.	Water uptake followed by rapid and enormous swelling.
Acrylic acid derivatives	Poly (acrylic acid) super porous hydrogel	Particle size - 106ìm. DT – 15 + 2 s	Wicking action
Effervescent mixture	Citric acid, tartaric acid, sodium bicarbonate.	Crystalline nature	Effervescence
Sodium alginate	Sodium salt of alginic acid	Slowly soluble in water, hygroscopic in nature	Swelling
L-HPC	Low hydroxy propyl cellulose	Particle size - 106ìm. DT – 90 s	Both swelling and wicking

Table-5 ODT Products Available in International Market.[62]

Brand name	Active ingredient	Company
Alavert	Loratadine	Wyeth Consumer Healthcare
Cibalginadue FAST	Ibuprofen	Novartis Consumer Health
Hyoscyamine Sulfate ODT	Hyoscyamine sulfate	ETHEX Corporation
NuLev	Hyoscyamine sulfate	Schwarz Pharma
Benadryl Fastmelt	Diphenhydramine	Pfizer
Nurofen flash tab	Ibuprofen	Boots Healthcare
Zomig ZMT & Rapimelt	Zolmitriptan	Astra Zeneca
Excedrin Quick Tabs	Acetaminophen	Bristol-Myers Squibb
Claritin RediTabs	Loratadine	Sching Corporation
Remeron SolTab	Mirtazepine	Organon Inc
Feldene Melt	Piroxicam	Pfizer
Propulsid Quicksolv	Cisapride monohydrate	Janssen
Imodium Instant melts	Loperamide HCL	Janssen

REVIEW OF LITERATURE

R. Mandrioli et al, [66] carried out Two different analytical methods for the quality control of fluoxetine in commercial formulations have been developed and compared: a spectrofluorimetric method and a capillary zone electrophoretic (CZE) method. The fluorescence emission values were measured at =293 nm when exciting at =230 nm. The CZE method used an uncoated fused-silica capillary and pH 2.5 phosphate buffer as the background electrolyte. The extraction of fluoxetine from the capsules consisted of a simple one-step dissolution with methanol/water, filtration and dilution. Both methods gave satisfactory results in terms of precision; the best results were obtained for the electrophoretic method, with RSD% values always lower than 2.0%. The accuracy was assessed by means of recovery studies, which gave very good results, between 97.5 and 102.6%. Furthermore, both methods also have the advantage of being very rapid.

Bernard A.Olsen et al, [67] carried out Chromatographic methods using chiral stationary phases have been developed for the separation of fluoxetine hydrochloride enantiomers. Ovomucoid and tris(3,5-dimethylphenyl carbamate) cellulose stationary phases were used in the reversed- and normal-phase modes, respectively. Acceptable isomer separation was achieved at pH 3.5 with the ovomucoid phase, but peak shapes were broad and the separation was quite sensitive to the acetonitrile concentration in the mobile phase. Isopropyl alcohol and methyl-tert-butyl ether mobile phase modifiers each provided complete resolution using the derivatized cellulose column. Better separation robustness was obtained with a column temperature of 1°C using the isopropyl alcohol modifier. The methyl-tert-butyl ether system was robust at room temperature. Differences in relative enantiomer amount of as little as 2% could be determined. The chromatographic conditions provided a much more discriminating test compared to an optical rotation method proposed for pharmacopeial use which had difficulty distinguishing

individual enantiomers. The chiral chromatographic conditions were also applied to capsule formulations to demonstrate the presence of racemic fluoxetine hydrochloride

Rubesh kumar et al, [68] carried out an analytical method development and validation of Fluoxetine HCl (FLU) and Olanzapine(OLZ) in bulk drug and pharmaceutical dosage form. The developed method is based upon simultaneous equations (Vierodt's) method by using UV/Visible spectroscopy. Both drugs come in the categories of anti- depressant and antipsychotic agent. The developed method can be used for the simultaneous estimation of FLU and OLZ in pharmaceutical dosage form without separating from each other or from the excipients. Primarily the ë max of Fluoxetine Hydrochloride (FLU) and Olanzapine (OLZ) was determined as 226 and 258 nm respectively. The suggested method is validated by using ICH validation parameters like accuracy, precession, linearity and LOD and LOQ respectively. This procedure was applied successfully for the analysis of FLU and OLZ in bulk drug and Pharmaceutical preparations.

Rajani Giridhar et al, [69] developed Two new rapid, sensitive and economical spectrophotometric methods are described for the determination of fluoxetine hydrochloride in bulk and in pharmaceutical formulations. Both methods are based on the formation of a yellow ion-pair complex due to the action of methyl orange (MO) and thymol blue (TM) on fluoxetine in acidic and basic medium, respectively. Under optimised conditions they show a absorption maxima at some particular nm with a particular molar absorptivities and Sandell's Sensitivities at a thousandth part of absorbance unit for MO and TB, respectively. The color is stable for 5 min after extraction. In both cases Beer's Law is obeyed at smaller concentrations with MO and TB. The proposal method was successfully extended to pharmaceutical preparations—capsules. The results obtained by both the agreement and E.P. (3rd edition) were in good agreement and statistical comparison by Student's t-test and variance ratio F-test showed no significant difference in the three methods.

M.A.Raggi et al, [70] carried out some analytical methods (two spectrophotometric and two chromatographic procedures) for the determination of fluoxetine in Prozac® capsules are described. All of them are applied to the samples after extracting the drug with a methanol–water mixture. The direct and derivative spectrophotometric methods are simple and reliable; the derivative method gives better recovery and lessens interference. Both methods show linearity in the 5–30 mg ml_1 range of the fluoxetine concentration range. Both HPLC methods (spectrophotometric and spectrofluorimetric detection) use a tetramethylammonium perchlorate buffer–acetonitrile mixture as the mobile phase and a C8 reversed phase column. The UV detection is performed at 226 nm, while the fluorimetric detection is performed by exciting at 230 nm and revealing the emission at 290 nm. The HPLC method with UV detection is more precise, but the procedure with fluorimetric detection is more sensitive.

Mohamad A.El-dawy at el, [71] developed a simple, accurate and sensitive high pressure liquid chromatographic technique is described for the determination of fluoxetine in the capsule dosage form, human plasma and in biological fluid. Analysis is performed with a reversed phase-C18 column with ultraviolet detection at 228 nm. The isocratic mobile phase (1.5 ml/min.) consists of acetonitrile and triethylamine buffer (48/52, V/V). A linear calibration model (correlation coefficient 0.99863) was developed using pyridoxine as internal standard. The retention times were 2.10 and 3.20 min for pyridoxine and fluoxetine, respectively. The method was applied for the quantitation of fluoxetine in spiked human plasma samples. The detection limit is 5 mg/l and the absorbance varies with fluoxetine concentrations in the range (10/300) mg/l. The mean % recovery9/S.D. was found to be 97.99%9/2.39. The proposed method was applied successfully for monitoring of fluoxetine in human plasma after single dose administration of one prozac

CH.Hareesha et al, [72] worked on Escitalopram Oxalate used as Antidepressant. The present investigation deals with the formulation of oral disintegrating tablets of baclofen that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. The odts were prepared by direct compression technique. It is observed in the formulations that comparing

micro crystalline cellulose with mannitol as a filling agent, mannitol shows better release of api

Kalpesh gur et al, [73]developed the fast disintegrating tablets of aceclofenac were prepared by subliming method with a view to enhance patient compliance. In this paper, two super-disintegrants, viz., crospovidone and sodium starch glycolate were used in different ratio (2-8 % w/w) with camphor (30 % w/w) as subliming agent. The prepared batches of tablets were evaluated for thickness, weigh variation, hardness, friability, drug content uniformity, wetting time, water absorption ratio, in-vitro disintegration time and in-vitro drug release. Based on disintegration time (approximately 21 second), three formulations were tested for the in-vitro drug release pattern (in ph 7.4 phosphate buffer). Among the three promising formulations, the formulation prepared by using 8% w/w of crospovidone and emerged as the overall best formulation based on the in-vitro drug release characteristics.

Uma vasi reddy et al, [74] compared the effect of superdisintegrants on the mouth dissolving property of salbutamol sulphate tablets. Orodispersible tablets of salbutamol sulphate of prepared using sodium starch glycollate, crosscarmellose sodium as superdisintegrants. The results revealed that the tablets containing subliming agent had a good dissolution profile. The optimized formulation showed good release profile with maximum drug being released at all time intervals. This work helped us in understanding the effect of formulation processing variables especially the Superdisintegrants on the drug release profile. The present study demonstrated potentials for rapid absorption improved bioavailability effective therapy and patient compliance.

Prameela rani. A et al, [75] metformin hcl (met.hcl) is an orally administered hypoglycemic agent, used in the management of non-insulin-dependent (type-2) diabetes. As precision of dosing and patient's compliance become important prerequisite for a long term antidiabetic treatment, there is a need to develop formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in administration while travelling and patient's

acceptability. Hence in the present study an attempt has een made to prepare fast disintegrating tablets of met.hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with isphagula husk, natural superdisintegrant and crosspovidone, synthetic superdisintegrant. The pure drug and formulation blend was examined for angle of repose, bulk density, tapped density, commpressibility index and haussner's ratio. The tablets were evaluated for hardness, tensile strength, drug content, friability and were found satisfactory. The disintegration time in the oral cavity was also tested and was found to be around 10sec. Based on dissolution rate the disintegrants can be rated as isphagula husk > crosspovidone. Hence ishagula husk was recommended as suitable disintegrant for the preparation of direct compression melt-in-mouth tablets of met.hcl. All the dissolution parameters were calculated and compared with market tablet. A 3.78 fold increase in the dissolution rate was observed with f4 formulation when compared to market tablet(glucophage). It was concluded that the rapidly disintegrating tablets with proper hardness, rapid disintegration in the oral cavity with enhanced dissolution rate can be made using Superdisintegrants.

Basani get al, [76] baclofen is a muscle relaxant and anti spastic. The present investigation deals with the formulation of oral disintegrating tablets of baclofen that disintegrate in the oral cavity upon contact with saliva and there by improve therapeutic efficacy. The odts were prepared by direct compression technique. The optimized formulation was also prepared by effervescent method. The influence of superdisintegrants, Crospovidone, croscaremellose sodium and sodium starch glycolate at three levels on disintegration time, wetting time and water absorption ration were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, in vitro dissolution, wetting time and water absorption ratio. The in vitro disintegration time of the best odts was found to be 14 sec and 28sec by direct compression and by effervescent method, respectively. Tablets containing crospovidone exhibit quick disintegration time than tablets containing croscaremellose sodium, sodium starch glycolate and effervescent mixture. Good correlation was observed between water absorption ratio and dt. The directly compressible rapidly disintegrating tablets of baclofen with shorter

disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

Jyotsana madan et al, [77] the objective of this work was to prepare and evaluate fast dissolving tablets of the nutraceutical, freeze dried aloevera gel. Fast dissolving tablets of the nutraceutical, freeze-dried aloevera gel, were prepared by dry granulation method. The tablets were evaluated for crushing strength, disintegration time, wetting time, friability, drug content and drug release. A 32 full factorial design was applied to investigate the combined effect of two formulation variables - amounts of microcrystalline cellulose and mannitol. The results of multiple regression analysis revealed that in order to obtain a fast dissolving tablet of the aloe vera gel, an optimum concentration of mannitol and a higher content of microcrystalline cellulose should be used. A response surface plot was also provided to graphically represent the effect of the independent variables on the disintegration time and wetting time. The validity of the generated mathematical model was tested by preparing a check point batch. This investigation has demonstrated that satisfactory fast dissolving aloe vera gel tablets can be formulated. It also showed the potential of experimental design in understanding the effect of formulation variables on the quality of fast dissolving tablets.

Jashanjit singh et al,[78] purpose: the objective of this study was to formulate and optimize an orodispersible formulation of meloxicam using a 2 factorial design for enhanced bioavailability.the tablets were made by non-aqueous wet granulation using crospovidone and mannitol. A 2 factorial design was used to investigate the amount of crospovidone and taste masking, soothening hydrophilic agent (mannitol), as independent variables, and disintegration time as dependent response. Formulated orodispersible tablets were evaluated for weight variation, friability, disintegration time, drug content, wetting time, water absorption ratio and in vitro drug release. The results show that the presence of a superdisintegrant and mannitol is desirable for orodispersion. All the formulations satisfied the limits of orodispersion with a dispersion time of less than 60 sec. For example, formulation f4 showed a disintegration time of 32.1 sec, crushing strength of 4.93 kg/cm2, drug content of 98.5% and fast drug release rate of 99.5% within 30 min, as compared

with the conventional tablet (49.5%) . It is feasible to formulate orodispersible tablets of meloxican with acceptable disintegration time, rapid drug release and good hardness, which could be amenable to replication on an industrial scale.

furtado et al, [79] showed a purpose of the present research was to the effect of camphor as a subliming agent on the mouth dissolving property of famotidine tablets. Method: orodispersible tablets of famotidine were prepared using camphor as subliming agent and sodium starch glycollate together with crosscarmellose sodium as superdisintegrants. The formulations were evaluated for weight variation, hardness, friability, drug content, wetting time, in vitro and in-vivo dispersion, mouth feel and in vitro dissolution. Result: all the formulations showed low weight variation with dispersion time less than 30 seconds and rapid in vitro dissolution. The results revealed that the tablets containing subliming agent had a good dissolution profile. The drug content of all the formulations was within the acceptable limits of the USP xxvii. The optimized formulation showed good release profile with maximum drug being released at all time intervals. Conclusion: this work helped in understanding the effect of formulation processing variables especially the subliming agent on the drug release profile. The present study demonstrated potentials for rapid absorption, improved bioavailability, effective therapy and patient compliance.

Anand et al,[80] prepared taste-masked orally disintegrating tablets (odts) of prednisolone (pdl) by incorporation of microspheres in the tablets for use in specifi c populations viz. Pediatrics, geriatrics and patients experiencing diffi culty in swallowing. Methods: microsphere containing pdl were prepared by the solvent evaporation method using acetone as solvent for ph-sensitive polymer and light liquid paraffi n as the encapsulating medium. Prepared microspheres were characterized with regard to the yield, drug content, particle size and size distribution, surface features, in vitro drug release and taste. Tablets, prepared by direct compression containing microspheres, were evaluated with regard to crushing strength, friability, disintegration time, drug content and in vitro drug release and taste. Results: the results obtained showed that the average size of microspheres is infl uenced greatly by the speed of stirring. Microspheres prepared by the solvent

evaporation method in acetone were of a regular spherical shape with satisfactory results in terms of the size and size distribution. The comparison of the dissolution profi les of microspheres in different media shows that microspheres produce a retarding effect in ph 6.8 buffer. Taste evaluation studies confirmed that microspheres of pdl having a drug to polymer ratio of 1: 10 are tasteless and these were further used for formulation into odts. Compression of microspheres resulted in breaking of a fraction of the microspheres but this didnot adversely affect the taste. Conclusion: effective taste-masking was achieved for pdl using the technique of Microencapsulation and odts of acceptable characteristics were obtained by disintegrant addition and direct compression.

Venkata ramana reddy S et al,[81] develop oral disintegrating tablets (odt) of low bitter hypertensive drugs like amlodipine besylate using tastem enhancers as a taste asking agents. Odt of amlodipine besylate were prepared using different superdisintegrants by direct compression method. Mannitol was used as a diluent and sodium lauryl sulphate was used as a wetting (surfactant) agent. Aspartame and acesulfame potassium were used for unpleasant taste masked from the amlodipine besylate by cosifting and serial of blending with other excipients. The mixed final blend was then compressed into tablets. The formulations were evaluated for weight variation, hardness, friability, wetting time, disintegrating time, dissolution, taste valuation study and in vitro dissolution. All the formulation showed low weight variation with different disintegration time and rapid in vitro dissolution. The results revealed that the tablets containing taste enhancers had a good palatability for the patients. The optimized formulation showed good taste masking, less disintegration time (<30seconds) and release profile with maximum drug being released at all time intervals. The present study demonstrated potentials for rapid disintegration in oral cavity without water, improved taste masking and patient compliance.

Anantha lakshmi pallikonda et al, [82] formulate and evaluate domperidone mdt's. It acts as an ant emetic used in the treatment of motion sickness. Different batches of tablets were prepared using higher and lower concentrations of superdisintegrants like croscarmellose sodium, crospovidone (c.p), sodium starch glycolate (ssg), while mcc was used as diluents. Tablets were prepared by slugging

method. Different evaluations tests like hardness, friability, wetting and disintegration times, % drug release were performed. Tablets containing along with crospovidone were disintegrate rapidly below 20sec and % drug release is 99% at 4th minute. Increased consumer satisfaction.

Mahaveer pr. Khinchi et al, [83] Superdisintegrants (such as ac-di-sol, crospovidone, sodium starch glycolate), diluents (dibasic calcium phosphate) along with sweetening agent (aspartame) were used in the formulation of tablets. The tablets were evaluated for hardness, friability, water absorption ratio, in-vitro disintegration time (dt), in-vitro disintegration time in oral cavity and in vitro drug release. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum dt were observed with crospovidone excipient prepared by direct compression.

Dr. Raghavendra rao n. et al, [84] carried out the study on novel co-processed Superdisintegrants were developed by solvent evaporation method using crospovidone and sodium starch glycolate in different ratios (1:1, 1:2 and 1:3) for use in the fast dissolving tablet formulations. The developed excipients were evaluated for angle of repose, carr's index and hausner's ratio in comparison with physical mixture of superdisintegrants. Fast dissolving tablets of felodipine were prepared using the above co-processed superdisintegrants and evaluated for pre-compression and postcompression parameters. Effect of co-processed superdisintegrants (such as crospovidone, and sodium starch glycolate) on wetting time, disintegrating time, drug content, in-vitro release, and stability parameters have been studied. From this study, it can be concluded that dissolution rate of felodipine could be enhanced by tablets containing co-processed superdisintegrant.

Suhas m. Kakade et al, [85] Orally disintegrating tablets prepared by direct compression and using Superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate designate, designated as three different groups of formulation (a, b and c) respectively were prepared and evaluated for the precompression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation,

friability, drug content, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, group (c) containing crospovidone emerged as the best formulation and showed maximum dissolution rate with 98.49% drug release in 15 min. All three groups of formulations released the drug at faster rates than that of marketed conventional tablets of sertraline.

Deshpande kiran bhaskar et al, [86] carrriedout the study was aimed, which can disintegrate or dissolve rapidly once placed in the oral cavity. Propranolol hydrochloride is a antihypertensive drug, which undergoes extensive hepatic degradation (96%), which have poor oral bioavailability (26%) for overcoming this problem orodispersible tablets of propranolol hydrochloride can be formulated which avoids extensive first pass metabolism and improvement in dissolution efficacy, disintegration time which results in improvement in bioavailability. The advantage of this formulation is such that in case of hypertension attack patient can take the drug without the usage of water. Therefore the main objective of the present work is to develop orodispersible tablets of propranolol hydrochloride to improve bioavailability, disintegration time, dissolution efficacy and patient compliance.

Tejash serasiya et al, [87] orodispersible tablets of pheniramine maleate were prepared by direct compression method using various superdisintegrants like crospovidone, croscarmellose sodium, sodium starch glycolate, low substituted hydroxypropyl cellulose, pregelatinized starch. The prepared tablets were evaluated for uniformity of weight, hardness, friability, wetting time, in-vitro disintegration time, in-vitro dispersion time and drug release study. All the formulation exhibited hardness between 3.3 – 3.6 kg/cm2. The tablets were disintegrating in–vitro within 20 to 51 sec. Dissolution studies revealed that formulations containing 10% crospovidone and formulation containing 10% croscarmellose sodium showed 100% of drug release, at the end of six min. The concentration of superdisintegrants had an effect on disintegration time and in-vitro drug dissolution whereas hardness and friability of resulting tablets were found to be independent of disintegrant concentration. The two formulations, one containing 10% of crospovidone and second containing 10% croscarmellose sodium were found to give the best results.

Pankaj p. Amrutkar et al,[88] Carried out the work on lamotrigine used in the treatment of depression and bipolar disorder. But it is a bitter drug and slightly soluble in water. Thus, in the work under taken, an attempt was made to mask the taste and to formulate into a chewable dispersible tablet by complexation with precirol ato-05, which also acts as taste masking agent. Since, these tablets can be swallowed in the form of dispersion; it is suitable dosage form for paediatric and geriatric patients. Drug-precirol ato-05 was prepared in drug to precirol ato-05 ratio of 1:2, 1:1.5, 1:1, 1:0.5. The prepared tablets were evaluated for general appearance, content uniformity, hardness, friability, taste evaluation, mouth feel, in vitro disintegration time, and in vitro dissolution studies. Tablets with precirol ato-05 have shown good disintegrating features, also, the dispersion not showing any bitter taste, indicate the capability of precirol ato-05 used, both as taste masking agents. Almost more than 90 percent of drug was released from the formulation within 1 h. Further formulations were subjected to stability testing for 3 months at temperatures 25±5°c/60±5%rh; 30±5°c/65±5%rh and 40±5°c/75±5%rh. Tablets have shown no appreciable changes with respect to taste, disintegration, and dissolution profiles.

Ganesh kumar gudas et al,[89]. Study an attempt has been made to prepare fast dissolving tablets of chlorpromazine hcl in the oral cavity with enhanced dissolution rate. The tablets were prepared with five superdisintegrants eg: sodium starch glycolate , crospovidone ,croscarmellose, l-hpc, pregelatinised starch , the blend was examined for angle of repose, bulk density, tapped density , compressibility index and hausners ratio. The tablets were evaluated for hardness, friability, disintegration time, dissolution rate, drug content, and were found to be within 1 min. It was concluded that the fast dissolving tablets with proper hardness, rapidly disintegrating with enhanced dissolution can be made using selected superdisintegrants.

Sradhanjali patra et al, [90] metronidazole is an antiemetic and prokinetic drug used in the treatment of motion sickness in adults and children.as precision of dosing and patient's compliance become important prerequisite for quick relief from motion sickness, there is a need to develop a formulation for this drug which overcomes problems such as difficulty in swallowing, inconvenience in

administration while traveling and better compliance. Hence in the present research work mouth dissolving tablets of metronidazole were developed with superdisintegrants like crospovidone, indion 414, l – hpc and pregelatinised starch in various concentrations like 8 % and 10 % w/w by wet granulation method. All formulations were evaluated for physical characteristics of compressed tablets such as weight variation, hardness, friability, drug content, disintegration time and in vitro dissolution study. Among all, the formulation f4 (containing 10% w/w concentration of crospovidone) was considered to be the best formulation, having disintegration time of 27 sec, hardness 2.56 kg/cm2 and in vitro drug release of 92.23% in 15 min. All the formulation follows higuchi order release kinetics.

Prajapati et al, [91] carriedout the work on piroxicam which has bad taste, half life of 30 hrs and poor water solubility. In the present work to develop taste masked orally disintegrating tablets of piroxicam, preformulation parameters like solubility, particle size, tapped density, bulk density,hausner ratio, carr's compressibility index, angle of repose, and differential scanning calorimetry study were performed. Out of twelve formulations (f-1 to f-12), f-11 formulation containing crospovidone xl 10 %, drug: polymer 1:0.35 , aspartame 6% and sodium lauryl sulphate 0.5%, showed optimum characteristics of orodispersible tablet (odt) of piroxicam with sufficient crushing strength (5.5 to 6.5 kp), friability (0.18%), wetting time (28 sec) and disintegration time (22 sec). In-vitro dissolution profile studies revealed that 82.3% drug was released within 5 min. The study concluded that crospovidone xl and eudragit epo can successfully be used as superdisintegrant and taste masking excipient respectively.

P***asupathi et.al,***[92].carried out the ork on lamotrigine chewable-dispersible tablet was prepared by using crosspovidone xl10, as a disintegrating agent, different grades of mannitol (pearlitol 160 c, pearlitol sd 200, pearlitol 500dc) as a diluents, pvp k30 as a binder and carried out studies for weight variation, thickness, hardness, content uniformity, disintegrating time, dispersion time, wetting time, in vitro drug release and stability study. Tablets were prepared by using direct compression method and wet granulation method. Furthermore, impact of different punches and superdisintegrants (sodium starch glycolate, and sodium crosscarmalose) were carried on f16 formulation.

Ashok Kumar et al,[93] investigation was to develop orally disintegrating tablets of terbutaline sulphate. Granules containing drug, diluent, subliming agents, aspartame were prepared by wet granulation technique using alcoholic solution of polyvinyl pyrrolidone K25 (10% w/v) as a binder. The dried granules were then mixed with lubricant magnesium stearate and glidant talc and compressed into tablets. Subliming agents was sublimed from the tablet by exposing it to drying at 65 0C. The tablets were evaluated for percentage friability, hardness, weight variation, disintegration time and percentage drug content. Menthol containing tablets resulted in rapid disintegration as compared with tablets containing ammonium bicarbonate and camphor. Formulations F4 showed the minimum disintegration time of 16s. Formulations tested for all the official tests for tablets and were found to be within limits.

Madhusudan rao Y et al, [94] deals with formulation of orodispersible tablets (ODT) of buspirone that disintegrate in the oral cavity upon contact with saliva and thereby should improve therapeutic efficacy. The ODTs were prepared by wet granulation and direct compression techniques. The optimized formulation was also prepared by freeze drying method. The influence of superdisintegrants, crospovidone, croscarmellose sodium and sodium starch glycolate at three levels on disintegration time, wetting time and water absorption ratio were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, *in vitro* dissolution, wetting time and water absorption ratio.

Pandey Shivanand et al,[95] development of taste masked orally disintegrating tablets are to increase patient compliance, ease of administration, safety and appropriate dosing. Orally disintegrating formulations also provide benefits for pharmaceutical companies like lifecycle management, line extension, market expansion, cost effective drug development programs. This technology has perceived faster onset of action (only if engineered for absorption in the oral cavity or stomach) as the dosage form is disintegrated prior to reaching the stomach and is ideal for acute diseases like hypertension and heart failure and particularly applicable to manage breakthrough symptoms. Fast dissolving tablets (FDT), tablet that disintegrates and dissolves rapidly in saliva without need of drinking water. The

FDT usually dissolve in the oral cavity in about 10 seconds to 3 minutes. Faster the drug goes into solution, the quicker absorption and onset of clinical effect.

PK Bhoyar et al,[96] present work was to mask the taste of ondansetron hydrochloride and to formulate its patient-friendly dosage form. Complexation technique using indion 234 (polycyclic potassium with carboxylic functionality) and an ion-exchange resin was used to mask the bitter taste and then the taste-masked drug was formulated into an orodispersible tablet (ODT). The drug loading onto the ion-exchange resin was optimized for mixing time, activation, effect of pH, mode of mixing, ratio of drug to resin and temperature. The resinate was evaluated for taste masking and characterized by X-ray diffraction study and infrared spectroscopy. ODTs were formulated using the drug–resin complex. The developed tablets were evaluated for hardness, friability, drug content, weight variation, content uniformity, friability, water absorption ratio, *in vitro* and *in vivo* disintegration time and in vitro drug release. The tablets disintegrated in vitro and in vivo within 24 and 27 s, respectively. Drug release from the tablet was completed within 2 min. The obtained results revealed that ondansetron HCl has been successfully taste masked and formulated into an ODT as a suitable alternative to the conventional tablets.

Shailesh Sharma et al,[97] formulate promethazine theoclate fast-dissolving tablets that offer a suitable approach to the treatment of nausea and vomiting The solubility of promethazine theoclate was increased by formulating it as a fast-dissolving tablet containing _-cyclodextrin, crospovidone, and camphor, using direct compression method. A 33 full factorial design was used to investigate the combined influence of three independent variables – amounts of camphor, crospovidone and _-cyclodextrin - on disintegration time, friability and drug release after 5 min. The optimization study, involving multiple regression analysis, revealed that optimum amounts of camphor, crospovidone and _-cyclodextrin gave a rapidly disintegrating/dissolving tablet. A Check point batch was also prepared to verify the validity of the evolved mathematical model. The optimized tablet should be prepared with an optimum amount of _-cyclodextrin (3.0 mg), camphor (3.2mg) and crospovidone (2.61 mg) which disintegrated in 30 s, with a friability of 0.60 % and drug release of 89 % in 5 min.

OBJECTIVE OF THE STUDY

Oral route of administration still has potential, as most preferred route because of its numerous advantages. The most popular oral dosage forms are tablets and capsules. However, one important drawback of these dosage forms is the need to swallow. Many patients express difficulty in swallowing tablets and hard gelatin capsules, resulting in non-compliance and ineffective therapy.

Recent advances in Novel Drug Delivery Systems (NDDS) aims to formulating a dosage form of drug molecules for convenient administration and to achieve better patient compliance. One such approach leads to development of oral disintegrating tablets.

Advantages of this drug delivery system include convenience of administration and accurate dosing as compared to liquids, easy portability, ability to provide advantages of liquid medication in the form of solid preparation, ideal for pediatric and geriatric patients and rapid dissolution/absorption of the drug, which may produce rapid onset of action. Some drugs are absorbed from mouth, pharynx and oesophagus as the saliva passes down into the stomach and in such cases bioavailability of the drug is increased: pre-gastric absorption can result in improved bioavailability and as result of reduced dosage, improved clinical performance through a reduction of unwanted effects.

A solid dosage form that dissolves rapidly in oral cavity, resulting in solution or suspension without the need of water is known as oral dissolving tablets. When this type of tablet is placed into the mouth, the saliva will serve to rapidly dissolve the tablet. They are also known as oro-dissolving, rapid – dissolve orodispersible, melt in mouth, rapimelt, quick dissolving tablets.

Conventional oral dosage forms like tablets, capsules are available in market but the major drawbacks with these are many patients find it difficult to

swallow (Dysphagia) tablets and hard gelatin capsules. The difficulty experienced in particular by pediatrics and geriatrics patients. Other groups that may experience problems include the mentally ill, mentally disabled and patients who are uncooperative and hence do not take their medicines as prescribed leading to patient noncompliance.

Fluoxetine Hydrochloride has been used for the treatment of anti pyscotic. It comes under BCS class 4 i.e., low solubility and low permeability and has biological half life (24-72 days). The administration of conventional tablet to psychotic patients is very difficult. Therefore need to develop suitable dosage form like Fluoxetine oral disintegrating tablet which may easy to administer to the psychotic patients.

The objective of this study is to design and development of fluoxetine oral disintegrant tablet by using different superdisintegrants like crospovidone, croscarmellose sodium and sodium starch glycolate. And also present work aims that effect on diluents on disintegration power and in vitro dissolution of the tablets.

PLAN OF WORK

The present work was carried out to formulate Oral Disintegrating Fluoxetine Hydrochloride tablets and to evaluate the invitro and stability studies for the prepared Fluoxetine Hydrochloride tablets. It was planned to carry out this work as outlined below.

- ✓ Characterization of drug substances and other excipients.
- ✓ Formulation development of Fluoxetine Hydrochloride Orally Disintegrating tablets by Direct Compression Technique.
- ✓ Evaluation of the pre compressional parameters.
- ✓ To evaluate the formulated Fluoxetine Hydrochloride tablets for the following parameters.
    a) Tablet thickness.
    b) Weight variation.
    c) Tablet friability.
    d) Wetting time.
    e) Tablet hardness.
    f) Assay
    g) Disintegration.
    h) Dissolution
- ✓ To carry out the stability studies for finalized formula of Orally Disintegrating Fluoxetine Hydrochloride Tablet as per ICH guidelines.

DRUG PROFILE [98,99,100]

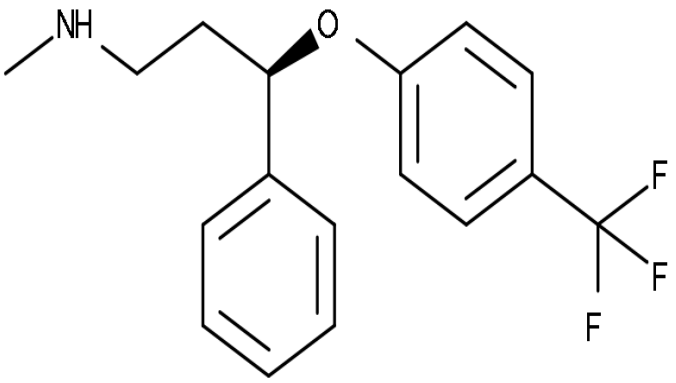
FLUOXETINE HYDROCHLORIDE

Category : Antidepressant agent

Chemical Name : (*RS*)-*N*-methyl-3-phenyl-3-[4-(trifluoromethyl)phenoxy]propan-1-amine

Description : A white to off white crystalline solid.

Molecular Structure



Molecular Formula : $C_{17}H_{18}F_3NO•HCL$

Molecular weight : 345.79

Bioavailability : 72%

Half life : 1-3 days (acute)

4-6 days (chronic)

Solubility : Soluble in methanol and ethanol, Sparingly soluble in acetonitrile, chloroform and acetone & slightly soluble in Dichloromethane, water and ethyl acetate.

Uses

Fluoxetine is an antidepressant (selective serotonin reuptake inhibitor-SSRI) used to treat depression, obsessive-compulsive disorder(bothersome thoughts that won't go away and the need to perform certain actions over and over), some eating disorders and panic attacks(sudden unexpected attacks of extreme fear and worry about these attacks). It is used to relieve the symptoms of premenstrual dysphoric disorder, including mood swing, irritability and bloating. It works by restoring the balance of certain natural substances (neurotransmitters such as serotonin) in the brain. Fluoxetine may improve your feelings of well-being and energy level and decrease nervousness.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metabolized to norfluoxetine, fluoxetine is a selective serotonin-reuptake inhibitor (SSRI), it blocks the reuptake of serotonin at the serotonin reuptake pump of the neuronal membrane, enhancing the actions of serotonin on $5HT_{1A}$ autoreceptors. SSRIs bind with significantly less affinity to histamine, acetylcholine, and norepinephrine receptors than tricyclic antidepressant drugs.

Pharmacodynamics

Fluoxetine, an antidepressant agent belonging to the selective serotonin reuptake inhibitors (SSRIs), is used to treat depression, bulimia nervosa, premenstrual dysphoric disorder, panic disorder and post-traumatic stress. According to the amines hypothesis, a functional decrease in the activity of amines, such as serotonin and norepinephrine, would result in depression; a functional increase of the activity of these amines would result in mood elevation. Fluoxetine's effects are thought to be associated with the inhibition of 5HT receptor, which leads to an increase of serotonin level.

Pharmacokinetics

The single- and multiple-dose pharmacokinetics of fluoxetine are linear and dose-proportional in a dose range of 10 to 40 mg/day. Biotransformation of fluoxetine is mainly hepatic, with a mean terminal half-life of about 1-3 days(acute),4-6 days(chronic). With once-daily dosing, steady state plasma concentrations are achieved within approximately one week.

Absorption and Distribution

Following a single oral dose (10 mg tablet or solution) of fluoxetine, peak blood levels occur at about 6-8 hours. Absorption of fluoxetine is not affected by food.

The absolute bioavailability of fluoxetine is about 72% relative to an intravenous dose, and the volume of distribution of fluoxetine is about 20 L/kg. Data specific on fluoxetine are unavailable.

The binding of fluoxetine to human plasma proteins is approximately 94.5%.

Metabolism and Elimination

Limited data from animal studies suggest that fluoxetine may undergo first-pass metabolism may occur via the liver and/or lungs. Fluoxetine appears to be extensively metabolized, likely in the liver, to norfluoxetine and other metabolites. Norfluoxetine, the principal active metabolite, is formed via *N*-demethylation of fluoxetine. Norfluoxetine appears to be comparable pharmacologic potency as fluoxetine. Fluoxetine and norfluoxetine both undergo phase II glucuronidation reactions in the liver. It is also thought that fluoxetine and norfluoxetine undergo *O*-dealkylation to form *p*-trifluoromethylphenol, which is then subsequently metabolized to hippuric acid.

The primary route of elimination appears to be hepatic metabolism to inactive metabolites excreted by the kidney.

Marked formulations **:** Adofen , Fluctin, Fluoxeren, Prozac

Table 6 - Drug Interactions

Cyclosporine	The antidepressant increases the effect and toxicity of cyclosporine
Amphetamine	Risk of serotoninergic syndrome
Phentermine	Risk of serotoninergic syndrome
Tramadol	The use of two serotonin modulators, such as fluoxetine and tramadol, may increase the risk of serotonin syndrome. Fluoxetine may decrease the effect of tramadol by decreasing active metabolite production.
Erythromycin	Possible serotoninergic syndrome with this combination
Eletriptan	Increased risk of CNS adverse effects
Ziprasidone	Additive QTc-prolonging effects may increase the risk of severe arrhythmias. Concomitant therapy is contraindicated.
Phenytoin	Fluoxetine increases the effect of phenytoin
Metoprolol	The SSRI, fluoxetine, may increase the bradycardic effect of the beta-blocker, metoprolol.
Dicumarol	The SSRI, fluoxetine, increases the effect of anticoagulant, dicumarol.
Atomoxetine	The CYP2D6 inhibitor could increase the effect and toxicity of atomoxetine
Zolmitriptan	Use of two serotonin modulators, such as zolmitriptan and fluoxetine, may increase the risk of serotonin syndrome. Consider alternate therapy or monitor for serotonin syndrome during concomitant therapy.
Dihydroergotamine	Possible ergotism and severe ischemia with this combination

Dosage

Usual adult dose for anxiety

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of one week.

Usual adult dose for depression

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of three weeks.

Usual pediatric dose for depression

12to17years

10 mg orally once a day in the morning or evening with or without food. The dose may be increased to 20 mg, after a minimum of three weeks.

EXCIPIENTS PROFILE[101,102]

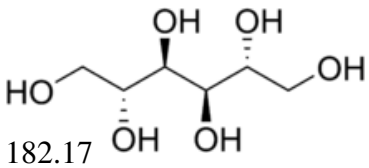
MANNITOL

Synonyms : Cordycepic acid, Manna sugar, D-mannite, Mannitolum; Mannogem.

Chemical Name : D-Mannitol

Empirical Formula : $C_6H_{14}O_6$

Structural Formula



Molecular Weight : 182.17

Functional Category : Plasticizer, sweetening agent, tablet and capsule diluent.

Solubility

Freely soluble in water, soluble in alkaline solutions, slightly soluble in pyridine, very slightly soluble in alcohol, practically insoluble in ether.

Applications in Pharmaceutical Formulation or Technology

Mannitol is widely used as a diluent (10–90% w/w) in tablet formulations, since it is not hygroscopic and may thus be used with moisture sensitive active ingredients. It may be used in direct compression tablet applications, for which the granular and spray dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. It is commonly used as an excipient in the manufacture of chewable tablet formulations and also used as a diluent in rapidly dispersing oral dosage forms.

Description

It occurs as a white, odourless, crystalline powder, or free flowing granules. It has a sweet taste and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol.

Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride.(19) Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/mL and 30 mg/mL concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminum, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect’.

CROSPOVIDONE

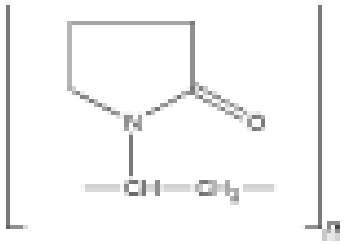
Synonyms

Crospovidonum, Crospopharm, crosslinked povidone, Kollidon CL, Kollidon CL-M, Polyplasdone XL, Polyplasdone XL-10, Polyvinyl polypyrrolidone.

Chemical Name **:** 1-Ethenyl-2-pyrrolidinone homopolymer

Empirical Formula

and Molecular Weight **:** $(C_6H_9NO)n$ >1000000



Functional Category **:** Tablet disintegrant

Solubility

Practically insoluble in water and in most common organic solvents.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water insoluble tablet disintegrant and dissolution agent used in tablets prepared by direct compression or wet and dry granulation methods. It can also be used as a solubility enhancer. Crospovidone can be used to enhance the solubility of poorly soluble drugs.

Description

Crospovidone is a white to creamy white, finely divided, free flowing, practically tasteless, odourless, hygroscopic powder.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level

Stability and Storage Conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

ASPARTAME

Synonyms

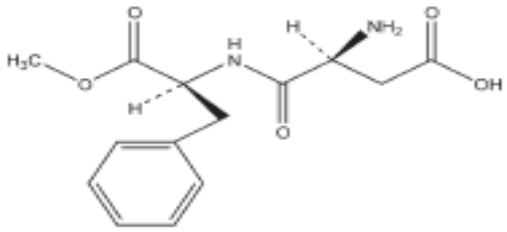
Aspartamum, Aspartyl phenylamine methyl ester, Natra Taste, NutraSweet, Pal Sweet, Pal Sweet Diet.

Chemical Name **:** N-L-a-Aspartyl-L-phenylalanine 1-methyl ester

Empirical Formula

and Molecular weight **:** $C_{14}H_{18}N_2O_5$; 294.30

Molecular Structure



Functional category **:** Sweetening agent.

Solubility

It is slightly soluble in ethanol (95%), sparingly soluble in water.

Applications in Pharmaceutical Formulation or Technology

It is used as a sweetening agent in tablets, powder mixes, and vitamin preparations. The approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal).

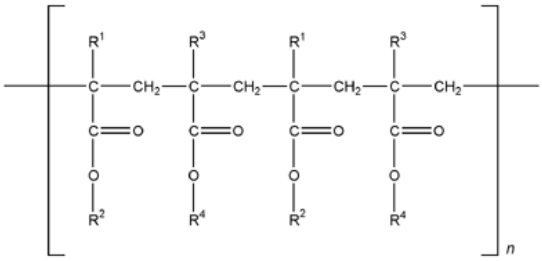
Description

It occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.

EUDRAGIT EPO

Synonyms **:** Methacrylic acid, eudragit.

Srtucture **:**



For Eudragit EPO

R1, R3 = CH3

R2 = CH2CH2N(CH3)2

R4 = CH3, C4H9

Chemical Name **:** Poly(butyl methacylate-co-(2-dimethylaminoethyl) methacrylate-co-methyl methacrylate) 1:2:1

Description

It is a white powder with a characteristic amine-like odour.

Characteristics

It shows low viscosity, high pigment binding capacity, Good adhesion.

Functional Category

Film forming agent, tablet binder, tablet diluents, Taste masking agent,

Glass Transition Temperatur (Tg) **:** ~48°C

Solubility **:** Soluble in gastric fluid up to pH 5.0

Typical Properties **:** Bulk density : 0.390 g/cm3

Tapped density : 0.424 g/cm3

Applications in Pharmaceutical Formulation or Technology:

Used as a plain or insulating film former. It is soluble in gastric fluid below pH 5.

Stability and Storage Conditions

Dry powder polymer forms are stable at temperatures less than 308C. Above this temperature, powders tend to form clumps, although this does not affect the quality of the substance and the clumps can be readily broken up. Dry powders are stable for at least 3 years if stored in a tightly closed container at less than 308C. Dispersions are sensitive to extreme temperatures and phase separation occurs below 08C. Dispersions should therefore be stored at temperatures between 5 and 258C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

Incompatability

Incompatibilities occur with certain polymethacrylate dispersions depending upon the ionic and physical properties of the polymer and solvent. For example, coagulation may be caused by soluble electrolytes, pH changes, some organic solvents, and extremes of temperature; Interactions between polymethacrylates and some drugs can occur, although solid polymethacrylates and organic solutions are generally more compatible than aqueous dispersions.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Additional measures should be taken when handling organic solutions of polymethacrylates. Eye protection, gloves, and a dust mask or respirator are recommended. Polymethacrylates should be handled in a well-ventilated environment and measures should be taken to prevent dust formation. Acute and chronic adverse effects have been observed in workers handling the related substances methyl methacrylate and poly- (methyl methacrylate) (PMMA).

SODIUM STARCH GLYCOLATE (SSG)

Synonyms

Carboxymethyl starch, Explotab, Primojel.

Functional Category

Tablet and capsule disintegrant.

Description

It is white to off-white, odourless, tasteless, free-flowing powder.

Solubility

It is practically insoluble in water; sparingly soluble in ethanol (95%). In water it swells upto 300 times its volume.

Incompatibilities

Incompatible with ascorbic acid

Stability and Storage

It is a stable material. It should be stored in a well closed container to protect from wide variations in humidity and temperature that may cause cracking.

Safety

It is generally regarded as a non-toxic and non-irritant material. However, oral ingestion of large quantities may be harmful.

Applications in Pharmaceutical Formulation and Technology

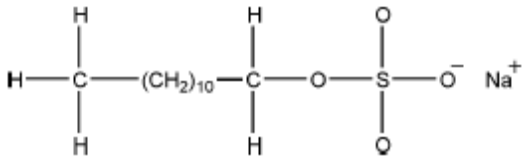
As a disintegrant in tablet (wet granulation and direct compression) and capsule formulation in 2-8% concentration.

Sodium lauryl sulfate

Synonyms

Dodecyl sodium sulfate; Elfan 240; sodium dodecyl sulfate; sodium laurilsulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; Texapon K12P.

Structure



Chemical name : Sulfuric acid monododecyl ester sodium salt.

Empirical formula : $C_{12}H_{25}NaO_4S$

Molecular weight : 288.38

Functional category :

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

Applications in Pharmaceutical Formulation and Technology:

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of non-parenteral pharmaceutical formulations like anionic emulsifier, forms self-emulsifying bases with fatty alcohols in concentrations (0.5-2.5%), as a skin cleanser in topical applications (1%), as a tablet lubricant (1–2%), as a wetting agent in dentifrices (1-2%).

Description

Sodium lauryl sulfate consists of white or cream to pale yellow colored crystals, flakes, or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

Melting point **:** 204–207^{o}C (for pure substance).

Solubility **:**

Freely soluble in water, giving an opalescent solution; practically insoluble in chloroform and ether.

Stability and storage conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e., pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation Solutions of sodium

lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze, and aluminum. Sodium lauryl sulfate is also incompatible with some alkaloidal salts and precipitates with lead and potassium salts.

CROSCARMELLOSE SODIUM (CCS)

Synonyms

Cross-linked carboxy methylcellulose sodium, Primellose, Solutab and Ac-Di-Sol

Functional category **:** Tablet and capsule disintegrant.

Description **:** Odorless and white coloured powder

Solubility **:**

It is insoluble in water. Although croscarmellose sodium rapidly swells to 4-8 times of its original volume on contact with water.

Incompatibilities

The efficacy of disintegrants, such as Croscarmellose sodium, may be slightly reduced in tablet formulations prepared by wet granulation or direct compression process which contain hygroscopic material such as sorbitol.

Stability and storage

Croscarmellose sodium is a stable though hygroscopic material. A model tablet formulation prepared by direct compression, with Croscarmellose sodium as disintegrant, showed no significant difference in drug dissolution after storage at 30^0C for 14 months

Safety

Croscarmellose is mainly used as a disintegrant in oral pharmaceutical formulations and is generally regarded as an essentially nontoxic and nonirritant

material. However, oral consumption of large amount of Croscarmellose sodium may have a laxative effect although the quantities used in solid dosage formulations are unlikely to cause such problems. .

Applications in pharmaceutical formulation and technology

Croscarmellose is used as a Superdisintegrant in capsules around 10-25% and also used in tablets between 0.5-5%

MATERIALS AND METHODS

LIST OF EQUIPMENTS

Table -7 List of Equipments used

Equipment	Manufacturer	Model
Electronic single pan balance	Sartorius Essae	LA1205 TE2145
Mechanical Sifter with sieve 40 and 60	Retsec	AS100
Tapped Density apparatus	Electro lab	ETD 1020
LOD	Satorious	MAB5
Analytical Sieve Shaker	Retsec	AS200
Blender	Rimec	410AG
Compression Machin	Chamundi Pharma Machinery	PPM406300210
Friabilator	Electro lab	Ef-2
Dissolution Apparatus	Electro lab	TDTO8L
Ultra voilet-visible spectroscopy	Shimadzu	UV 2400PC series
Disintegration Apparatus	Electro Lab	ED2AL
Moisture analyzer	Sartorius	---
pH meter	Eutech cyber scan 100	---

LIST OF CHEMICALS

Table 8 - List of Chemicals used

Ingredients	Supplier
Fluoxetine hydrochloride	Merck Pvt.Ltd
CrosPovidone CL-F	Merck Pvt.Ltd
Eudrogit Epo	Merck Pvt.Ltd
Croscarmolose sodium	Merck Pvt.Ltd
Sodium Starch Glycolate	Merck Pvt.Ltd
Aspartame	Merck Pvt.Ltd
Microcrystalline cellulose	Merck Pvt.Ltd
Mannitol SD200 (Peritol)	Merck Pvt.Ltd
Sodium Lauryl sulfate	Merck Pvt.Ltd
Peppermint flavour	Merck Pvt.Ltd
Aerosil	Merck Pvt.Ltd
Talc	Merck Pvt.Ltd

7.1 PREFORMULATION STUDIES

Standard calibration curve of the Fluoxetine Hydrochloride

10mg of the dug was dissolved in the 50ml of methanol and sonicated for few minutes and further diluted to 100ml with methanol. From this above solution further dilutions were carried out to obtained 5, 10, 15, 20, 25 µg/ml using methanol. The absorbance of the above concentration was measured at 226nm using UV spectroscopy.

Bulk Density[1]

It's a measurement to describe packing of particles. Bulk density/apparent density is used to determine the amount of drug that occupies the volume (gm/ml).

$$Bulk\ Density = \frac{Mass\ of\ the\ blend}{Untapped\ volume}$$

Determination of Bulk density

Weighed accurately the quantity of blend was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by the drug was measured. Bulk density was measured by using formula $\rho_b = m / V_b$. The results were shown in the table-15.

Tapped density[103]

Powder blend was taken in 100 ml measuring cylinder that was placed in Electro lab tapped density apparatus (method USP-I). Initial volume (V_0) of the cylinder was noted and then the cylinder was tapped 250 times and volume was measured. Then further an additional 500 tapings were repeated. No difference was noted between the volumes of the two tapings (250 and 500). The final volume (V) was considered after completion of 500 taps. Tapped density was measured by using formula $\rho_t = m / V_t$. The results were shown in the table-15.

Compressibility Index[103,104]

Powder blend was transferred to 100ml-graduated cylinder and subjected to 250 & 500taps in tap density tester (Electro lab). The difference between two taps should be less than 2%. The % of compressibility index calculated using formula

$$\text{Compressibility Index} = 100 * (\rho_{tapped} - \rho_{bulk}) / \rho_{tapped}$$

Hausner's ratio[103]

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5. It is determined by ratio of tapped density and bulk density.

Hausners ratio = $\rho_{tapped} / \rho_{bulk}$

Table 9 - Scale of Flowability

Compressibility index (%)	Flow character	Hausner Ratio
≤10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very poor	1.46 – 1.59
>38	Very, very poor	>1.60

Angle of repose[103]

It is defined as the maximum angle that can be obtained between the free standing of powder heap and horizontal plane, angle of repose calculated by using given formula

$$\text{Angle of repose} = \tan^{-1}\left(\frac{\text{heigh of the pile}}{\text{radius of the pile}}\right)$$

Procedure

Powder blend was passed through a funnel kept at a height 2 cm from the base. The powder passed till it forms a heap and touches the tip of the funnel. The radius was measured and angle of repose was calculated by using the above formula.

Table -10 Flow Properties and Corresponding Angle of Repose

Flow Property	Angle of Repose (degrees)

Excellent	25 – 30
Good	31 – 35
Fair – aid not needed	36 – 40
Passable – may hang up	41 – 45
Poor - must agitate, vibrate	46 – 55
Very poor	56 – 65
Very, very poor	>66

From the above results it is evident that the drug has poor flow properties, as the compressibility index, Hausner's ratio and Angle of repose values are high.

Melting point: melting point was carried by capillary tube method.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Drug-Excipient compatibility studies lay the foundation for designing a chemically stable formulation for clinical and commercial development. Drug excipient compatibility studies are conducted during preformulation to select the most appropriate excipients.

The compatibility studies were performed between Fluoxetine hydrochloride and excipients with different ratios as given in Table 10.

Table-11 Compatibility Study Ratio for Solid Dosage Forms

S.NO	Ingredients	Ratio
1	Fluoxetine Hydrochloride	
2	Fluoxetine Hydrochloride + Eudragit EPO	1:1
3	Fluoxetine Hydrochloride + Crospovidone CL-F	1:0.5
4	Fluoxetine Hydrochloride + croscarmolse sodium	1:0.5
5	Fluoxetine Hydrochloride + Aspartame	1:0.5
6	Fluoxetine Hydrochloride + sodium starch glycolate	1:0.5
7	Fluoxetine Hydrochloride + micro crystalline cellulose	1:10
8	Fluoxetine Hydrochloride + mannitol	1:10
9	Fluoxetine Hydrochloride + Aerosil	1:0.05
10	Fluoxetine Hydrochloride + sodium lauryl sulfate	1:0.1
11	Fluoxetine Hydrochloride + peppermint flavour	1:0.05
12	Fluoxetine Hydrochloride + Talc	1:0.05

The active ingredients and the excipients were mixed in the selected ratios using a mortor and pestle. The mixtures was transferred into glass vials and sealed.

The samples were placed as first set of initial samples and second set of samples were kept at 40°C±2°C/75%±5 % RH for 4 weeks. The samples were analyzed by IR and DSC analysis.

7.2 MANUFACTURING PROCESS

Formulation of oral disintegrating tablets of Fluoxetine Hydrochloride 10 mg was carried out by direct compression technique. Eudragit EPO was melted at 70°C and then Fluoxetine Hydrochloride was added and continued stirring for 5 min then the blend was cooled and passed through 80# mesh. Other excipients passed through 40# mesh and added to drug and Eudragit mixture. The final blend was mixed thoroughly and compressed with 6mm flat bowled edge punch. The composition of different formulation was shown in the table-12.

Table-12 Formulation Developmental Trails

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Fluoxetine Hydrochloride	10	10	10	10	10	10	10	10	10
Eydragit Epo	10	10	10	10	10	10	10	10	10
Croscarmolose sodium	5	5	5	0	0	0	0	0	0
Sodium starch glycolate	0	0	0	5	5	5	0	0	0
Crospovidone	0	0	0	0	0	0	5	5	5
Micro crystalline cellulose	68	34	0	68	34	0	68	34	0
Mannitol	0	34	68	0	34	68	0	34	68
Aspartame	5	5	5	5	5	5	5	5	5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium lauryl sulfate	1	1	1	1	1	1	1	1	1
Peppermint flavour	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Talc	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Total weight(mg)	100	100	100	100	100	100	100	100	100

7.3 POST COMPRESSION PARAMETERS

PHYSICAL APPEARANCE

The physical appearance of the compressed tablets involves the measurement of a number of attributes like tablet shape, smoothness, chipping, cracks, surface texture, colour etc.

THICKNESS

Thickness was determined for 20 pre-weighed tablets of each batch using a digital vernier scale and the average thickness was determined in mm**.** The tablet thickness should be controlled within a ± 5% variation of a standard.

WEIGHT VARIATION

20 tablets were selected randomly from a batch and were individually weighed and then the average weight was calculated. The tablets meet the USP specifications if not more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limits.

HARDNESS TEST

The crushing load which is the force required to break the tablet in the radial direction was measured using a Schluenzier hardness tester. The hardness of 10 tablets was noted and the average hardness was calculated. It is given in kp or kg/cm^2.

PERCENTAGE FRIABILITY

In friability testing the tablets are subjected to abrasion and shock. It gives an indication of the tablets ability to resist chipping and abrasion during transportation and shipping.

Method

10 tablets were taken and initial weight was noted. The tablets were rotated in the Roche Friabilator for 100 revolutions at 25 rpm. The tablets were dedusted and reweighed.

The percentage friability is expressed as the loss of weight and is calculated by the formula:

$$\%Friability = \frac{(Intial\ weight\ of\ tab - Final\ weightof\ tab)}{Final\ weightof\ tab} \times 100$$

The percentage friability should be not more than 1%w/w of the tablets being tested.

DISINTEGRATION TIME

Disintegration time is the time taken by the tablet to breakup into smaller particles. The disintegration test was carried out in an apparatus containing a basket rack assembly with six glass tubes of 7.75 cm in length and 2.15 mm in diameter, the bottom of which consists of a #10 mesh sieve. The basket is raised and lowered 28-32 times per minute in a medium of 900 ml which is maintained at 37±2^{0}C. Six tablets were placed in each of the tubes and the time required for complete passage of tablet fragments through the mesh (# 10) was considered as the disintegration time of the tablet. The disintegration time that patients can experience for oral disintegrating tablets ranges from 5 to 30seconds.

WETTING TIME

Wetting time of dosage form is related to with the contact angle. Wetting time of the ODT is another important parameter, which needs to be assessed to give an insight into the disintegration properties of the tablet. Lower wetting time implies a quicker disintegration of the tablet. The wetting time of the tablets can be measured by using the simple procedure[73]. Five circular tissue papers of 10cm diameter was placed in a petridish. Ten milliliters of water soluble dye solution is added to petridish. A tablet was carefully placed on the surface of the tissue paper.

The time required for water to reach upper surface of the tablet was noted as the wetting time. For measuring water absorption ration the weight of the tablet before keeping in the petridish is noted (Wb). The wetted tablet from the petridish is taken and reweighed (Wa). The water absorption ratio*R,* can be the determined according to the following equation.

$$R = 100 \text{ (Wa-Wb) / Wb}$$

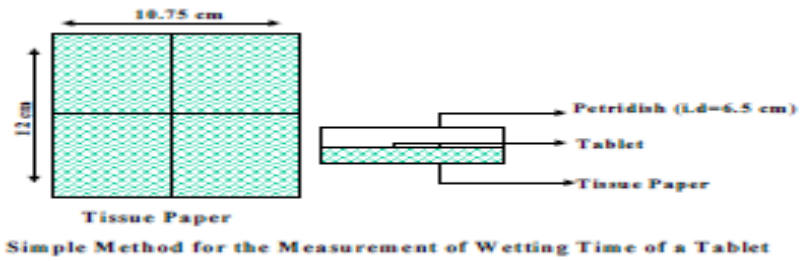


Figure 10 Illustration of wetting time

DISSOLUTION STUDIES

Dissolution is a process by which the disintegrated solid solute enters the solution. The test determines the time required for a definite percentage of the drug in a tablet to dissolve under specified conditions.

Method

The dissolution test was carried out in USP Apparatus Type II (paddle) with 1000ml of 1.2 pH as the dissolution medium. The samples were drawn at 5, 10, 15, 30 and 45 min. Fresh volume of the medium were replaced with the withdrawn volume to maintain the sink conditions. Samples withdrawn and were analyzed for the percentage of drug released.

Dissolution Parameters

Dissolution Apparatus	**:**	USP Apparatus Type II (Paddle)
Dissolution Medium	**:**	0.1 M Hcl
Volume	**:**	1000 ml
Temperature	**:**	37±2° C
Rpm	**:**	100
Sampling Intervals (min)	**:**	5, 10, 15,30and 45min

CONTENT UNIFORMITY

About 12 tablets were grinded to fine powder in a dry mortar and a quantity of powder equavalent to 100mg of Fluoxetine Hydrochloride was transferred into 100ml volumetric flask. To this 50ml of methanol was added and sonicated to dissolve the drug and diluted to volume with methanol and mixed thoroughly. The solution was filtered through what man filter paper no 1.and futher diluted to get a requied ppm

UV parameters

Instrument Type	:	UV – 2400PC series
Measuring mode	:	Absorbance
Wavelength range	:	200.00nm to 300.00nm
Scan speed	:	Medium
Slit width	:	2.0nm

Calculation

$$\frac{Sample\ absorbance}{Standard\ absorbance} \times \frac{Standard\ dilution}{Sample\ dilution} \times \frac{Average\ Weight}{Label\ claim} \times 100$$

STABILITY STUDIES

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors, such as temperature, humidity etc.

Accelerated study studies of the product was carried out at 40°C±2°C/75% ±5% RH for 2 months. The samples were analysed drug content, hardness, friability and disintegration time, dissolution.

RESULTS AND DISCUSSION

STANDARD CALIBRATION CURVE

Table13- Standard Calibration Curve of the Fluoxetine Hydrochloride

Concentration(µg/ml)	Absorbance at 228nm
0	0
5	0.196
10	0.370
15	0.591
20	0.81
25	0.985
Slope(m)	0.0395
Intercept	0.003
correlation	0.9985

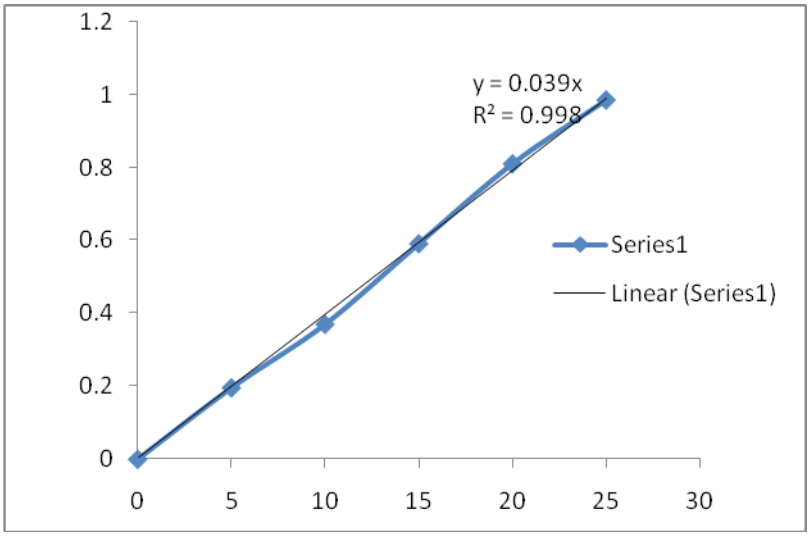


Figure-11 Standard calibration curve of the Fluoxetine Hydrochloride

Table -14 Raw Material Analysis of the Fluoxetine Hydrochloride Drug

TEST	SPECIFICATION	RESULT
Description	A white to half white crystalline solid	A white crystalline

		solid
Melting point (^{0}C)	Between 179-182	180.5to 183.9
Solubility	Soluble in methanol and ethanol, sparingly soluble in acetonitrile, chloroform and acetone and slightly soluble in dichloromethane and ethyl acetate	Compiles
Assay (%)	NLT 98.0%& NMT 102.0%	99.7%

Raw Material analysis of Fluoxetine Hydrochloride

The raw material analysis of the Fluoxetine Hydrochloride was carried out and the results were shown in table 14.

Table-15 Flow Properties of Fluoxetine Hydrochloride

S.NO	TEST	RESULT
1	Bulk density(g/ml)	0.238
2	Tap density(g/ml)	0.374
3	Compressibility Index (%)	36%
4	Hausner Ratio	1.57
5	Angle of Repose	48.71

The results indicate that flow property of the drug was found very poor.

CHARECTERISATION OF PREFORMULATION BLEND

Table-15 Results of Pre Compression Parameters

BATCH NOS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Angle of repose	29.78	28.22	27.13	30.91	29.06	28.01	28.98	28.74	27.58

Bulk density	0.629	0.601	0.584	0.487	0.526	0.599	0.564	0.571	0.586
Tap density	0.728	0.697	0.651	0.590	0.610	0.680	0.659	0.667	0.662
Compressibility index	13.59	13.77	10.29	17.45	13.77	11.91	14.41	14.39	11.48
Hausner's ratio	1.21	1.15	1.11	1.21	1.15	1.13	1.17	1.16	1.13

The flow property of blend was determined by Angle of repose, Bulk Density, Tap Density, Compressability Index and Hauser's ratio. The results were shown in Table-14 and 15. It indicates that flow property of powder blend was increased after addition of excipients such as mannitol, crospovidone.

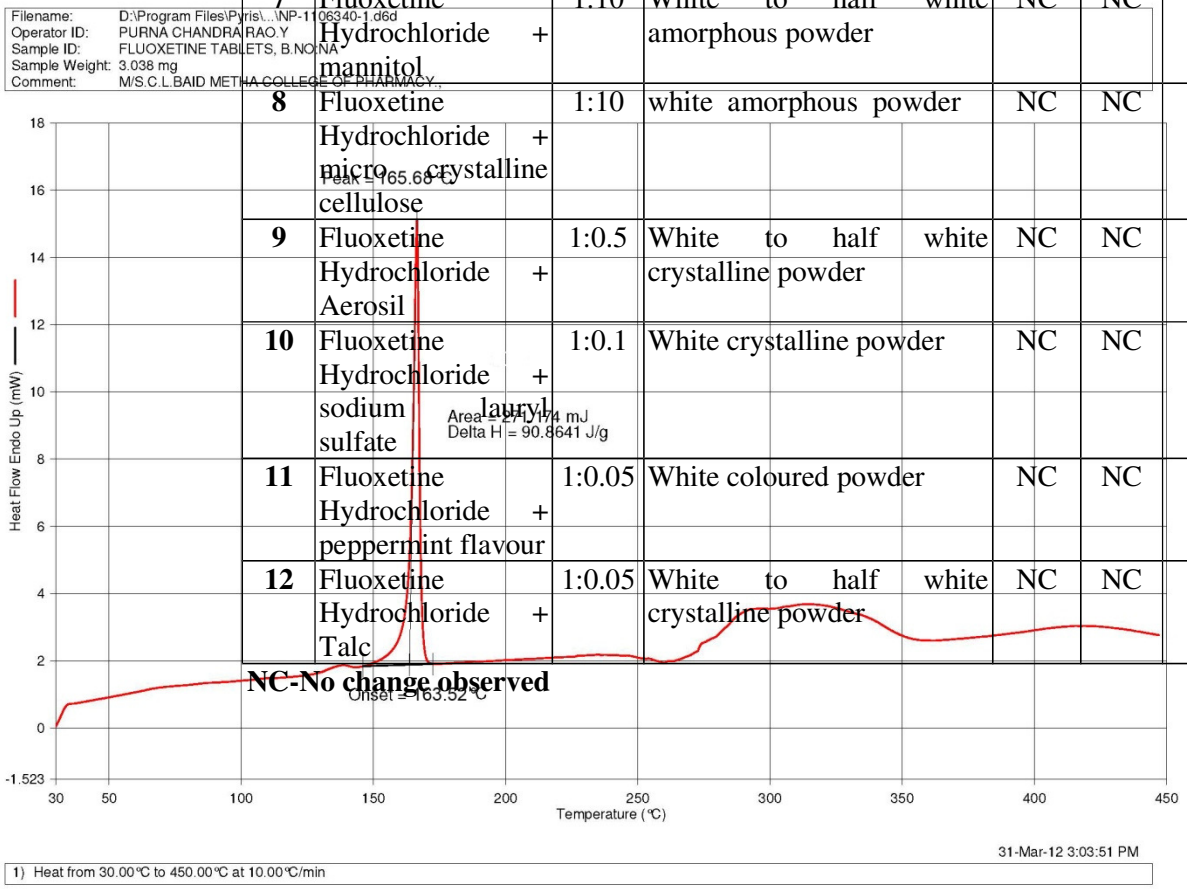
DRUG-EXCIPIENT COMPATIBILITY STUDIES

a) PHYSICAL OBSERVATION

Table-16 Physical Observation of Drug and Excipients

S.no	Ingredient	Ratio	Description				
			Initial	Final 40°C±2°C/75%±5			
				I week	II week	III week	IV week
1	Fluoxetine Hydrochloride		White to half white crystalline solid	NC	NC	NC	NC
2	Fluoxetine Hydrochloride + Eudragit Epo	1:1	White to half white crystalline powder	NC	NC	NC	NC
3	Fluoxetine Hydrochloride + Crospovidone CL-F	1:0.5	White to half white crystalline powder	NC	NC	NC	NC
4	Fluoxetine Hydrochloride + croscarmolose sodium	1:0.5	White to half white crystalline powder	NC	NC	NC	NC
5	Fluoxetine Hydrochloride + sodium starch glycolate	1:0.5	White to half white crystalline powder	NC	NC	NC	NC
6	Fluoxetine Hydrochloride + Aspartame	1:0.5	White to half white crystalline powder	NC	NC	NC	NC
7	Fluoxetine Hydrochloride + mannitol	1:10	White to half white amorphous powder	NC	NC	NC	NC
8	Fluoxetine Hydrochloride + micro crystalline cellulose	1:10	white amorphous powder	NC	NC	NC	NC
9	Fluoxetine Hydrochloride + Aerosil	1:0.5	White to half white crystalline powder	NC	NC	NC	NC
10	Fluoxetine Hydrochloride + sodium lauryl sulfate	1:0.1	White crystalline powder	NC	NC	NC	NC
11	Fluoxetine Hydrochloride + peppermint flavour	1:0.05	White coloured powder	NC	NC	NC	NC
12	Fluoxetine Hydrochloride + Talc	1:0.05	White to half white crystalline powder	NC	NC	NC	NC

NC-No change observed



B) FTIR ANALYSIS OF DRUG AND EUDRAGIT EPO

IR SPECTRUM OF FLUOXETINE HYDROCHLORIDE

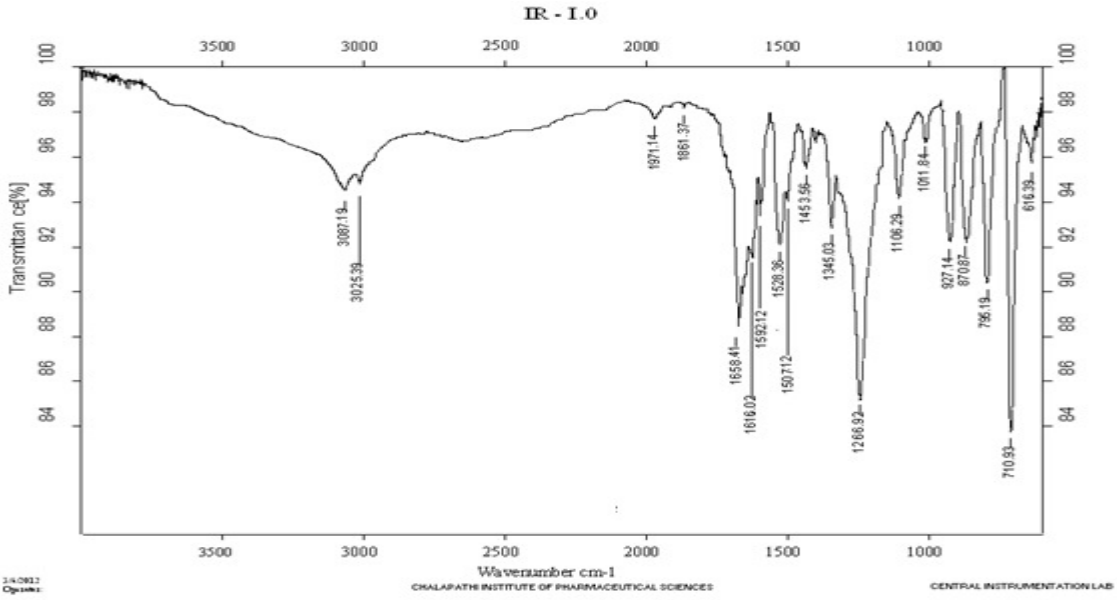


Figure 12 FTIR of fluoxetine hydrchloride

IR SPECTROSCOPY OF FLUOXETINE AND EUDRAGIT EPO

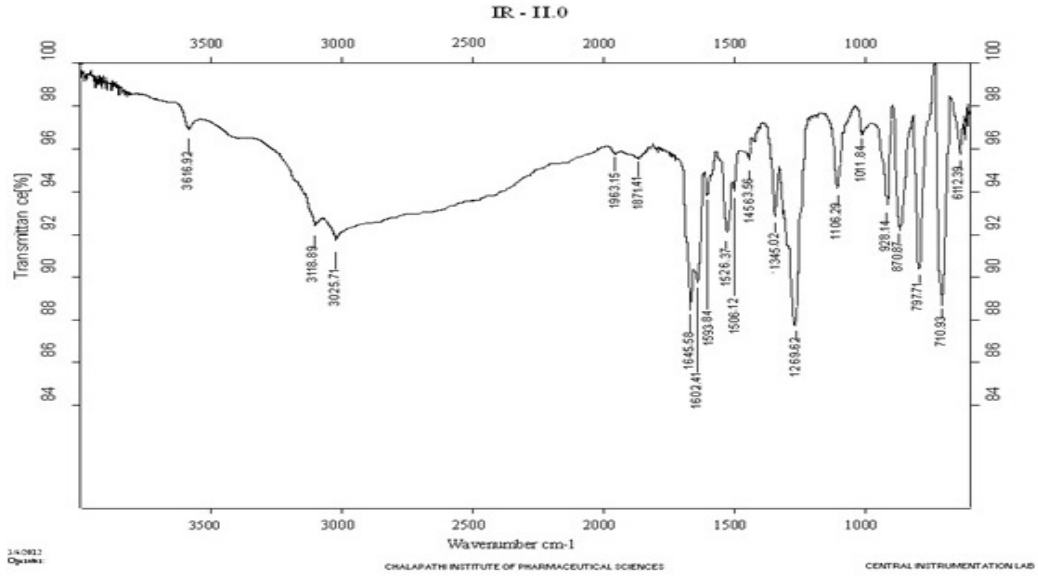


Figure 13 FTIR of Fluoxetine and Eudragit EPO

C) DSC ANALYSIS OF DRUG AND EUDRAGIT EPO

DSC OF FLUOXETINE HYDROCHLORIDE

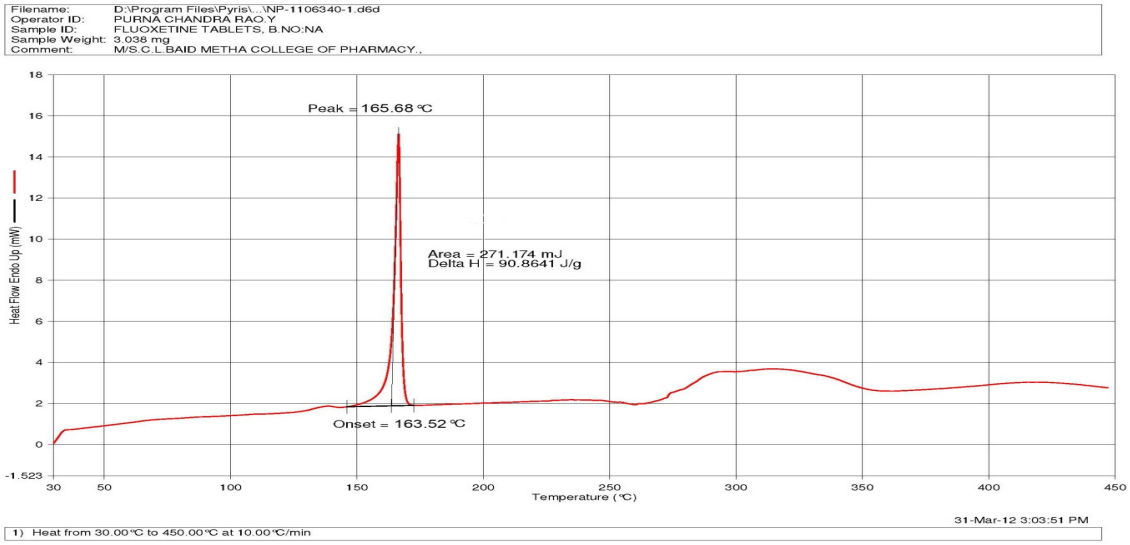


Figure 14 DSC of Fluoxetine Hydrochloride

DSC OF DRUG AND EUDRAGIT EPO

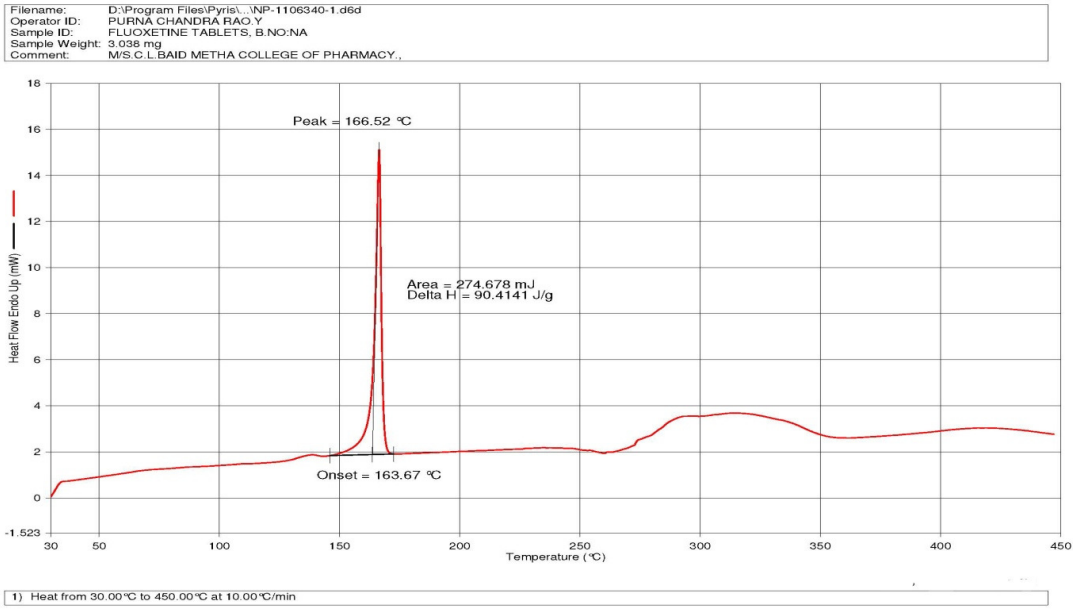


Figure 15 DSC of Drug and Eudargit EPO

The results of physical observation were given in the table 16. The results indicate that there is no physical properties change in the drug and excipients.

FTIR spectra of Fluoxetine Hydrohloride showed peaks at 1658, 1528, and 1345cm^{-1}. Spectrum of drug + Eudragit EPO showed peaks at 1645, 1526 and 1345 cm-^{1}. The results indicate that there is no interactions between the drug and Eudragit EPO. DSC analysis of fluoxetine shown a single sharp exothermic effect **Tpeak = 165.68 ºC** and ΔHt = 90.8641 J/g. thermogram of drug and Eudragit EPO mixture were shown a single exothermic peak **Tpeak = 166.52º C** and ΔHt = 90.4141 J/g. There is no change in exotherm of pure drug of fluoxetine in drug and Eudragit EPO mixture. The results indicate that drug and Eudragit EPO are compatible.

POST COMPRESSION PARAMETERS

Table-17 Results of Post-Compressional Parameters

Physical Appearance :- white colored tablets without break line

Formulation Code	Average weight (mg) ±7.5 %	Thickness (mm) ±5%	Hardness (kp)	Percentage Friability (%) 0.1-0.9%	In vitro Disintegration Time (sec) (±3)	Wetting time (sec) (±3)	Content uniformity
F1	101	2.85	3.1	0.31	62	68	89.24%
F2	99.6	2.84	3.1	0.20	59	64	90.47%
F3	101.5	2.73	3.5	0.17	58	56	92.25%
F4	100	2.81	3	0.60	69	72	82.14%
F5	98.5	2.85	3.1	0.34	66	69	83.35%
F6	102.1	2.89	3.4	0.24	64	62	85.9%
F7	100	2.87	3.1	0.21	17	19	96.84%
F8	100	2.91	3.4	0.13	15	16	97.25%
F9	100	2.90	3.5	0.09	13	12	99.14%

Disintegration time

Results of disintegration time were shown in Table 17. F9 formulation was showed quick dissolution time of 13 (±3) sec. Result indicate that mannitol and Superdisintegrant crospovidone was increased disintegration time of the tablets.

Wetting time

Wetting time of the formulation is shown in Table 17. The results indicate that F9 showed very less wetting time (12±3 sec). Reason could be Superdisintegrant crospovidone was increased porous structure in the tablets.

***in vitro* DISSOLUTION STUDY**

TABLE-18 I*n vitro* Dissolution Study of Fluoxetine Hydrochloride Oral Disintegrating Tablets

Cumulative percentage of drug release (%)									
Time (min)	**F 1**	**F 2**	**F 3**	**F4**	**F5**	**F6**	**F7**	**F 8**	**F9**
0	0	0	0	0	0	0	0	0	0
5	25.13	25.79	26.61	16.23	21.28	24.86	31.76	33.12	36.25
10	48.41	49.37	55.71	36.49	37.14	41.62	57.65	57.54	61.04
15	77.49	78.12	81.72	70.33	72.59	74.2	81.51	83.29	87.71
30	84.35	85.14	88.27	78.47	80.02	82.52	89.75	89.79	93.26
45	89.24	90.47	92.25	82.14	83.35	85.9	96.84	97.25	99.14

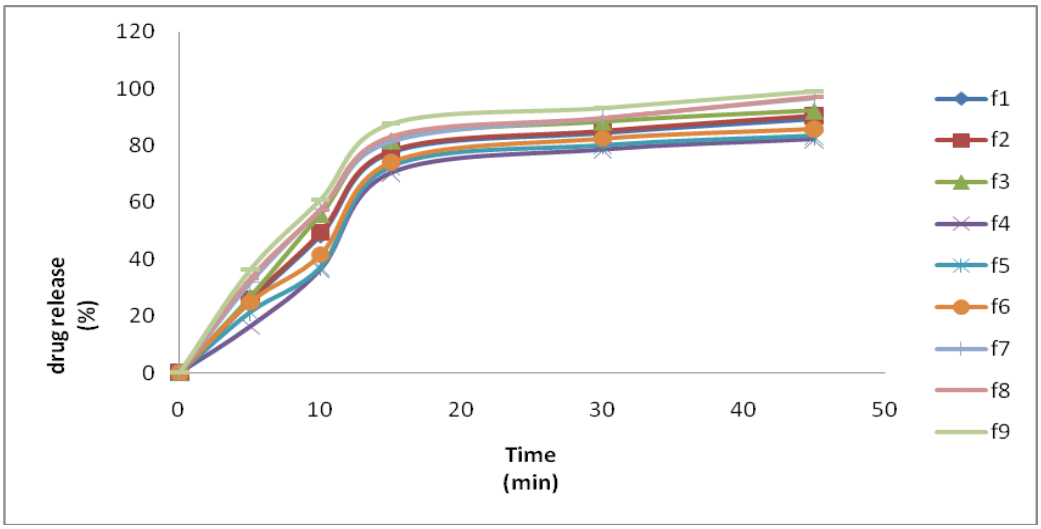


Figure 12 ***in vitro*** **Dissolution study of Fluoxetine Hydrochloride Oral Disintegrating Tablet**

In vitro **Dissolution study**

In vitro dissolution profiles of the all formulations were shown in Table 17. Formulation F9 was showed maximum drug release 99.14% in 45 min. The reason could be the formulations contains superdisintegrant crospovidone (5%), it can provide more porous structure and water wicking capacity in the tablets.

STABILITY STUDIES

RESULTS OF STABILITY DATA

Table: 19 Stability Study Data

PARAMETERS TESTED	**STORAGE CONDITIONS**		
	INITIAL	**$40^0C \pm 2^0C$ / 75% ±5% RH**	
		1st month	**2nd month**
Description	White colored round tablet with out break line	No change	No change
Average weight (mg)	101	101	101
Thickness (mm)	2.87	2.87	2.86
Hardness (kp)	3.5	3.5	3.3
% Friability	0.09	0.12	0.17
Disintegration time (sec)	15	18	20
Assay	99.7	99.8	99.5

Table-20 Dissolution Data of Stability Study Sample(Percentage of Drug Release)

Time Interval (min)	Initial	$40^0C \pm 2^0C$ / 75% ±5% RH	
		Ist month	2nd month
0	0	0	0
5	36.25	36.71	35.78
10	61.04	61.29	60.81
15	87.71	87.91	87.12
30	93.26	93.12	91.98
45	99.14	99.01	98.72

Stability data of fluoxetine orodispersible tablets were shown in Table 19. Stability study is conducted for the optimized formulation F9. The results indicate that there is no change in the formulation after two months at 40°C/75%RH.

CONCLUSION

Fluoxetine HCL orodispersible tablet was developed by using various superdisintegrant. Formulation contains crospovidone and mannitol showed quick disintegration behavior. In vitro release profile indicates that formulation F9 showed better release of drug. It is concluded from the above study that 5%w/w crospovidone as Superdisintegrant and mannitol as filler most suitable for preparation of fluoxetine Hydrochloride oral disintegrating tablet.

Short term stability study of Fluoxetine Hydrochloride orally disintegrating tablet was carried out for 2 month at 40°C/75%RH. Results of stability study revealed that no change was observed in formulation throughout the stability study. It can be concluded that fluoxetine hcl orodispersible tablet may have good shelf life.

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